Economic evaluations of antidepressant treatments a national cohort study in Taiwan

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Abstract

Given the marked personal, social and economic impacts, depressive disorder creates significant demands on individuals, health service providers and society as a whole. Antidepressant drugs remain the mainstay of treatment for depression for most people in contact with healthcare services and the last 20 years have seen dramatic changes in antidepressant prescription patterns. Initially, there was an increase in the use of the selective serotonin reuptake inhibitors (SSRIs) and subsequently, other novel antidepressant agents with different pharmacological mechanisms entered the market. Given the range of choices, clinicians must decide about which is the most appropriate intervention for their patients. To this end, knowledge regarding the relative cost-effectiveness and cost-utility of individual antidepressants is important. Therefore, in this thesis, a systematic review was first conducted to assess methodological approaches in economic evaluations of pharmacological treatments using database analyses. Based on the National Health Insurance Research Database in Taiwan, a cost analysis was conducted to identify which demographic and clinical characteristics are associated with healthcare costs of patients with depression. Compared to patients prescribed SSRIs, those prescribed older antidepressants had lower total and psychiatric costs, while patients prescribed serotonin norepinephrine reuptake inhibitors (SNRIs), and other newer antidepressants had higher total and psychiatric costs. The baseline comorbidities of cardiovascular diseases (CVD) and headache were also associated with healthcare costs over the 12-month period. To further assess the longer-term economic impacts, a set of database outcome statuses (sustained treatment-free status, continuous treatment, and late re-contact) were then applied to explore factors associated with outcome status following initial treatments

and to examine healthcare costs over the following three years by outcome status. The results showed the initial outcome status could exert an impact on total healthcare costs in the second and third years after commencing treatments. Finally, cost-effectiveness and cost-utility were compared between different categories of antidepressant treatments and also to test whether and how the presence of CVD, the most prevalent comorbid physical illness in this cohort, affects these results. The results showed that SSRIs are more cost-effective than tricyclic antidepressants and SNRIs regardless of comorbid CVD. There are various limitations to be considered in these analyses, including the limited scope of costs, the lack of clinical information, and the adoption of utility scores from previous studies. Further efforts to elucidate the relationship between depression treatments, costs and outcomes for longer period of follow up are warranted.

Contributors

The analyses in this thesis were all student-initiated. Yi-Ju Pan designed the study, conducted the literature review and statistical analyses, interpreted the results, as well as wrote the first draft of this thesis. Prof. Ling-Ling Yeh gave suggestions and helped with database management. Prof. Martin Knapp contributed to interpretations of some of the results. Prof. Paul McCrone contributed to study design and interpretations of some results. Yi-Ju Pan and Prof. Paul McCrone proof the current version of this thesis.

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List of Abbreviations

CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CUA	Cost utility analysis
CVD	Cardiovascular disease
DALY	Disability-adjusted life-year
DM	Diabetes mellitus
EQ-5D	EuroQol five-dimension questionnaire
GAD	Generalised anxiety disorder
GLM	Generalised linear model
HDRS	Hamilton Depression Rating Scale
ICD	International Classification of Diseases
ICER	Incremental cost-effectiveness ratio
MADRS	Montgomery-Asberg Depression Rating Scale
MAOI	Monoamine oxidase inhibitor
MDD	Major depressive disorder
NDRI	Norepinephrine dopamine reuptake inhibitor
NHI	National health insurance
NHIRD	National health insurance research database
NTD	New Taiwan Dollar
OR	Odds ratio
PPP	Purchasing power parity

PPS	Painful physical symptoms
QALY	Quality-adjusted life-year
RCT	Randomised controlled trial
RMSE	Root mean square error
RR	Relative risk
SF-6D	Short form-6D
SG	Standard gamble
SNRI	Serotonin norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant
TTO	Time trade-off

List of Publications

Main publications:

- Pan YJ, Knapp M, McCrone P (2012): Cost-effectiveness comparisons between antidepressant treatments in depression: evidence from database analyses and prospective studies. *Journal of Affective Disorders* 139(2): 113-25
- Pan YJ, Knapp M, Yeh LL, Chen YP, McCrone P (2013): Treatment costs for depression with pain and cardiovascular comorbidities. *Journal of Psychiatric Research* 47(3): 329-36
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Related publications:

- Pan YJ, Liu SK, Yeh LL (2013): Factors affecting early attrition and later treatment course of antidepressant treatment of depression in naturalistic settings: an 18-month nationwide population-based study. *Journal of Psychiatric Research*. 47(7):916-25

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I hope this thesis will be useful to someone who is interested in conducting economic evaluations in the future.

Chapter 1. Introduction

1.1. Aims and objectives

The overall aim of this thesis is to apply methods of economic evaluation to assess costs, treatment outcomes, and cost-effectiveness of pharmacological treatment for patients with depression in Taiwan.

The specific objectives are:

- To describe the epidemiology of depressive disorders and to summarise existing literature on the treatment and consequences of depressive disorders.
- To undertake a systematic review of published economic evaluations of pharmacological treatments for patients with depression to identify existing methods and any gaps in the current knowledge.
- To identify and critically appraise study designs, outcome measures and methods of economic evaluation for pharmacological treatments of depression in naturalistic settings.
- To identify and develop appropriate methods for estimating treatment outcomes and cost-effectiveness of pharmacological treatments of depression using a database analysis.
- To report the treatment costs of depression and to identify patient characteristics (demographic and clinical, including physical comorbidities) associated with these costs.
- To assess the impact of treatment outcomes on future service use and costs.
- To conduct a cost-effectiveness and cost-utility analysis of pharmacological

treatment for depression with a particular focus on the impact of physical comorbidities.

1.2. What is depression?

Depression is characterised by low mood, lack of interest, and a range of associated emotional, cognitive, physical and behavioural symptoms. The identification of *major depressive disorder* (MDD) is based not only on its severity but also on persistence, the presence of other symptoms (e.g. change in appetite and sleep), and the degree of functional and social impairment (NICE, 2010). Mood usually remains low throughout the course of each day in patients with MDD. However, mood may vary diurnally for some people, with gradual improvement throughout the day; for others, mood may be reactive to positive events, but these elevations in mood are not sustained. Typical behavioural/physical symptoms include irritability, social withdrawal, and exacerbation of pre-existing pains, a lack of libido, fatigue and diminished activity (Gerber et al., 1992). While there can be reduced sleep and appetite, for some people sleep and appetite are increased. A loss of enjoyment or interest in everyday life is common, as is suicidal ideation, actual suicide attempts or completed suicides. Cognitive changes include reduced concentration, negative thoughts about oneself, one's past and the future, mental slowing and rumination (Cassano and Fava, 2002). In sum, MDD exists when a persistent low mood is accompanied by a range of other symptoms; the number and combination needed to make a diagnosis being operationally defined (APA, 1994; WHO, 1992).

Onset and course

Although the first episode of MDD may occur at any time from early childhood through to old age, the majority of people have their first episode during early adulthood but another substantial proportion of people have their first episode in childhood or adolescence (Fava and Kendler, 2000; Zisook et al., 2007). Individuals may experience a range of symptoms in the months prior to the full illness, including anxiety and milder depressive symptoms; others may develop severe depressive illness rapidly, not uncommonly following a stressful life event (Brown et al., 2010). Somatic symptoms may sometimes dominate the clinical picture, leading the clinician to first investigate possible underlying physical illness until mood changes become obvious. Although depression is highly prevalent in clinical settings, patients may tend to report somatic symptoms rather than emotional sufferings. Besides, the presence of somatic symptoms with depression may not increase the recognition or treatment of depression by physicians (Williams et al., 2003).

Regarding course of illness, a meta-analysis (221 patients from 19 trials) showed that 20% of untreated patients with MDD improved within four to eight weeks, and 50% improved within six months; the authors also estimated that 60% of responders to placebo and 30% of responders to antidepressants may experience spontaneous resolution of symptoms if untreated (Posternak and Miller, 2001). An earlier study followed up 114 patients with untreated depression for six months and found that the mean duration of an episode was six months, with 50% remission by 25 weeks (Coryell et al., 1994). When treated by psychiatrists with antidepressants, another study showed that the median time to recovery for MDD patients was three months,

with 26% recovering within one month, 63% within three months, 85% within one year, and 88% within two years (Furukawa et al., 2000). Further studies following patients with depression treated in general practice settings reported a 67.5% rate of recovery during the first six months (Bottomley et al., 2010).

Despite a relatively high rate of initial recovery, incomplete recovery and relapse are common for patients with depression in the longer-term follow-up. An earlier study showed that only 30% of recovered patients remained in recovery and symptom-free during a one-year follow-up (Keller and Shapiro, 1981). The WHO study of mental disorders (15 centres, 14 countries) also found that 50% of patients still had a diagnosis of depression after one year (Simon et al., 2002). Evidence suggested that at least 10% of depressed patients suffer from persistent or chronic depression (Kessler et al., 2003). Following the first episode of MDD, at least 50% of people would have at least one more episode and, after the second and third episodes, the risk of further relapse rises to 70% and 90%, respectively (Kupfer, 1991). People with early onset depression and depression occurring in old age have a significantly increased vulnerability to relapse (Giles et al., 1989; Mitchell and Subramaniam, 2005). Early onset depression seems to imply a genetic influence on disease course and findings related to old age depression may underline the importance of assessing other risk factors related to patients' age. Therefore, while the outlook for people with a first episode seems favourable, the likelihood of recurrent episodes over the long term can be high with many patients experiencing depressive symptoms and functional impairments over many years (Akiskal, 1986).

Disability and mortality

Globally, depression is a major cause of disability. In 1990, it was the fourth most common cause of disability-adjusted life years (DALYs) in the world, and it is projected to become the second most common cause by 2020 (World Bank, 1993). It was previously estimated that about 1.5 million DALYs were lost each year in Western countries due to depression (Murray et al., 1994). A dose-response relationship between depression severity and the extent of disability has also been proposed (Ormel and Costa e Silva, 1995). In patients essentially disability free at baseline, depressive illness resulted in a 1.5-fold (at three months) and a 1.8-fold (at 12 months) increase in risk of onset of physical disability, after controlling for physical disease severity. Depressive illness also resulted in a 2.2-fold (at three months) and a 23-fold (at 12 months) increase in risk of onset of social disability (Ormel et al., 1999).

There are major impacts of depression on social as well as occupational functioning (Hirschfeld et al., 2000; Kessler et al., 1999a). Social impairments include reduced ability to communicate and sustain relationships. Emotional, motivational and cognitive effects of the illness can substantially reduce a person's ability to work effectively, with losses in personal and family income as well as lost contributions to society in terms of his/her employment skills and tax revenues. Wider social effects may include greater dependence upon welfare benefits. For example, depressed workers in the USA reported 1.5-3.2 more work-absence days per month compared to people who were not depressed (Kessler et al., 1999a), while in the European Study of the Epidemiology of Mental Disorders, depressed workers had three to four times

more work-loss days per month (Alonso et al., 2004a). Notwithstanding the impact of absenteeism, the greatest cost associated with MDD results from presenteeism or reduced productivity while at work (Lerner and Henke, 2008). Taken together, MDD is among the most costly of all health problems to employers in terms of work absence and productivity loss (Hilton et al., 2010).

Depression can exacerbate the pain, distress and disability associated with physical health problems. More specifically, depression combined with chronic physical health problems incrementally worsens health compared with physical disease alone or even combinations of physical diseases (Moussavi et al., 2007). For a range of physical health problems, findings suggest an increased risk of death in the presence of comorbid depression (Cassano and Fava, 2002). For instance, depression is associated with an 80% increased risk, both of the development of coronary heart disease and of subsequent mortality in established disease (Nicholson et al., 2006). The relationship between depression and chronic physical disorders will be discussed in more detail in Section 1.4.

Although with substantial variation between countries, suicide is another important issue that accounts for nearly 1% of all deaths in the general population, with around two-thirds of this figure occurring in individuals with depression (Sartorius, 2001). Having depression leads to a more than four times risk of suicide than for the general population, and the difference is nearly 20-fold in the most severely ill (Bostwick and Pankratz, 2000). The National Comorbidity Survey in the USA found that patients with MDD had an odds ratio of 11 for suicide ideation and of 9.6 for suicide plans (Kessler et al., 1999b; Kessler et al., 1994). Overall, the actual lifetime risk of suicide

in MDD may be estimated at between 3.4% and 6% (Nierenberg et al., 2001). In addition, the National Comorbidity Study reported a lifetime prevalence of at least one comorbid disorder in 74% of patients with depression, including anxiety disorders (58%) and substance use disorders (39%) (Kessler et al., 1996). Depression is also frequently prevalent in patients with schizophrenia and other psychiatric disorders (Enns et al., 2001). It is noteworthy that comorbidity with other mental disorders such as anxiety disorders may further aggravate suicide risk (Angst et al., 1999).

Prevalence

With disparities attributable to the method of assessment and real differences between countries, estimates of the proportion of people who are likely to experience depression in their lifetime vary widely between studies and settings, but the best estimates may lie between about four and 10% for MDD, and between about 2.5 and 5% for dysthymia (Waraich et al., 2004). Prevalence rates have consistently been found to be between 1.5 and 2.5 times higher in women than men (Waraich et al., 2004).

The prevalence of MDD varies widely across different cultures (Andrade et al., 2003; Weissman et al., 1996). In the 1980s, the lifetime prevalence of MDD as determined by the Diagnostic Interview Schedule (DIS) ranged from 1.1% in Taiwan to 19% in Beirut (Hwu et al., 1996; Weissman et al., 1996). In the 2000s, the estimated lifetime prevalence of MDD increased in most countries, but considerable cross-national variability in the lifetime prevalence of MDD still existed (Andrade et al., 2003; Kessler et al., 2003; Weissman et al., 1996). For example, the International

Consortium of Psychiatric Epidemiology (ICPE) representing 10 countries reported lifetime prevalence rates of MDD from 3% in Japan to 16.9% in the USA (Andrade et al., 2003). Over the past decades, lower prevalence rates of MDD have been reported among Asian countries in several cross-national surveys. For example, a more recent survey (conducted between 2003 and 2005), the Taiwan Psychiatric Morbidity Survey (TPMS) (Liao et al., 2012), reported a 1.2% life-time prevalence rate for MDD in a nationally representative sample of 10,135 adult individuals using a face-to-face interview with the paper version of the World Mental Health Survey of the WHO Composite International Diagnostic Interview (WMH-CIDI) (Kessler and Ustun, 2004).

Apart from the significantly lower prevalence of MDD as a disease entity in Asian countries than in the West, the prevalence rates of individual MDD symptoms have been reported to be lower in Taiwan and Korea, than in the USA when comparing the nationally representative samples of TPMS, the Korean Epidemiologic Catchment Area Study and the National Comorbidity Survey (Chang et al., 2008; Liao et al., 2012). There are a range of explanations for the lower prevalence of MDD in non-Western countries. One school of thought is that the diagnostic threshold of MDD (e.g. DSM) may be higher as people in these non-Western countries may not show positive responses to individual symptoms of MDD as often as Westerners do and the administration of identical diagnostic measures may identify different levels of depression across cultures (Simon et al., 2002). For instance, individuals with MDD in Taiwan reported more lost workdays, ranging from 5.8 for no impairment to mild impairment to 61.3 for those with severe impairment. Their counterparts in the US study had figures of 2.1 and 53.5 respectively (Liao et al., 2012). Similarly,

Koreans diagnosed with MDD also showed more work impairment than Americans with MDD in their nationally representative samples (Chang et al., 2008). Although lost workdays can be influenced by labour market conditions, the finding that the severity and the associated functional impairments of MDD diagnosed using the same diagnostic measures may be greater in these Asian countries warrants further research (Chang et al., 2008; Liao et al., 2012).

Cultural stoicism has been used to explain the lower prevalence of MDD in the Taiwanese population; when a Western-designed structured diagnostic interview is applied to people who tend to repress their feelings, the culturally determined 'response bias' may lead to a lower estimate of the prevalence of emotional problems (Compton et al., 1991). Usually, cultural stoicism refers to a relatively high tolerance for or denial of emotional sufferings in these cultures (Hwu et al., 1996). This hypothesis is supported by the finding that greater acculturation is associated with a greater tendency to report persistent and impairing depressive episodes among Chinese people living in Australia (Parker et al., 2005). This stoicism in Taiwanese adults may be also reflected in the much lower percentage of help-seeking behaviours; only 20% of patients with MDD in a nationally representative sample sought help (mental health, general medical, health care, human services, or complementary/alternative medicine) in the previous year (Liao et al., 2012), compared to 57.3% in the USA (Kessler et al., 2003). After stratification by severity, the percentages of MDD cases ever seeking professional help in the TPMS (0% for mild severity and 21.7% for moderate severity or above) remained much lower than in the US study (35.2% for mild severity and 54.6-70.5% for moderate severity or above) (Kessler et al., 2003). Consistently, based on claims data from the National Health

Insurance system in Taiwan, the one-year prevalence of treated MDD was found to be only 0.35% (Chien et al., 2004). In addition, the percentage of MDD cases (68.9%) who reported low perceived need as the reason for not seeking professional help in TPMS was higher than the 25.9% reported in the US National Comorbidity Survey-Replication (Mojtabai et al., 2011). The tendency that low prevalence of diagnosed MDD accompanied by low help-seeking behaviour is found not only in Taiwan but also in China, Korea and Japan (Chang et al., 2008; Lee et al., 2007; Naganuma et al., 2006), which poses a great challenge regarding depression treatment for policy-makers, health providers and society in these countries.

1.3. Pharmacotherapy of depression

Although pharmacological, psychological, and case management interventions are all recommended, antidepressant drugs remain the mainstay of treatment for depression (NICE, 2009). The last 20 years have seen dramatic change in antidepressant prescription patterns all over the world. Initially, there was an increase in the use of the selective serotonin reuptake inhibitors (SSRIs), which produced a progressive rise in total drug expenditures for antidepressants (Barbui et al., 2001; Lexchin et al., 2003). Other novel antidepressant agents with different pharmacological mechanisms have also entered the market over the past decades.

The placebo effect in trials of psychiatric medications is a concern. Sometimes the placebo effect is so large that specific pharmacological effects can be hard to identify. There can also be suspicion of publication bias, especially in pharmaceutical company funded trials (Lexchin et al., 2003; Melander et al., 2003). In general, antidepressants

for depression may offer little or no advantage over placebo for patients with subthreshold depressive symptoms or mild depression, who often improve spontaneously or respond well to non-specific measures such as emotional support and education. However, the evidence does support the efficacy of pharmacological treatments with more severe and persistent depression. Systematic reviews using meta-analyses suggest that antidepressant drugs, when considered individually or by class, are more effective than placebo in the treatment of MDD (Gartlehner et al., 2008; NICE, 2004). SSRIs are considered to be safer in overdose than tricyclic antidepressants (TCAs) and are generally better tolerated than antidepressants from other classes. SSRIs are recommended as first-line pharmacological treatment of moderate to severe depression in England and Wales (NICE, 2004), and are now the most commonly prescribed antidepressants in many countries (including Taiwan, see Table 4.1). However, there are still concerns over side effects, which potentially limit patients' adherence. SSRIs as a class are associated with headache and gastrointestinal symptoms, and a relative higher propensity than other antidepressants to cause hyponatraemia and sexual dysfunction. TCAs tend to be associated with anticholinergic side effects and a higher likelihood than other antidepressants to cause adverse cardiovascular effects including hypotension, tachycardia and corrected QT interval (QTc) prolongation. Venlafaxine (a serotonin norepinephrine reuptake inhibitor (SNRI)) may be reported to be better tolerated than TCAs but side effects like nausea and headache are not uncommon; withdrawal symptoms when stopping venlafaxine abruptly sometimes occur. Some of the common antidepressant side effects, such as nausea, tend to resolve within the first week of treatment whereas others, such as anticholinergic effects and, in some patients, sexual dysfunction, may persist.

Antidepressant treatment has been reported to be associated with an increased risk of suicide, particularly in adolescents and young adults, leading to the recommendation that patients should be warned of this potential adverse effect during the early weeks of treatment. All antidepressants have been implicated in this risk. Although the relative risk of developing suicidal thoughts and acts may be elevated above placebo rates in some patient groups, the absolute risk remains very small and is similar between all antidepressants (Schneeweiss et al., 2010). Overall, evidence suggests that the most effective way to prevent suicidal thoughts and acts is still to treat depression (Gibbons et al., 2012).

Despite major developments in the management of depressive disorder, in clinical practice, incomplete, or lack of, response to treatment continues to be problematic. Many studies have demonstrated that approximately one-third of patients treated for depression do not respond satisfactorily to first-line pharmacotherapy. Follow-up observations reveal that a considerable number of patients have a poor prognosis and as many as 20% remain unwell two years after the onset of illness (Keller et al., 1986). Even after multiple treatments, up to 10% of patients remain depressed (Nierenberg and Amsterdam, 1990). A number of studies suggest that between 10 and 20% of patients with depression have a long-term poor outcome (Lee and Murray, 1988; Winokur et al., 1993). Recent evidence has emphasised that clinicians should be aware that clinical improvement starts immediately after commencing treatment; early improvement is a strong predictor of eventual response which is unlikely if no improvement is evident after four weeks of treatment (Anderson et al., 2008; Posternak and Zimmerman, 2005). At the present time, there are a variety of strategies for improving efficacy following initial non-response, including dose escalation,

switching to another antidepressant, and combining the antidepressant with another antidepressant, a second drug such as lithium, a second generation antipsychotic drug or thyroid hormones. Adjunctive use of psychological therapies, particularly cognitive behavioural therapy (CBT), is also supported.

An untreated depressive episode typically lasts about six months (Angst and Preisig, 1995; Solomon et al., 1997) and, in view of the high recurrence rate if antidepressant medication is stopped immediately after response, it is recommended that antidepressant treatment is continued for a minimum of six months after remission of MDD and the same dose of antidepressant is used in this continuation phase. It is also recommended that patients with recurrent MDD should continue to receive maintenance treatment (NICE, 2004). There is evidence that patients with residual symptoms are at increasing risk of relapse of MDD and the current practice aims to achieve remission to prevent future relapses.

Pharmacotherapy of depression in Taiwan

Health care in Taiwan is organised through a government administered system, which provides national health insurance (NHI) to all the population. Citizens are eligible to receive comprehensive medical care, including preventive health services, clinical care, hospitalisation, residential care, and social rehabilitation. Taiwan launched this compulsory single-payer NHI programme on 1 March 1995. In 2003, there were 21.9 million (the population in Taiwan is about 23 million) individuals enrolled in the NHI – a coverage rate of 96%. The NHI contracted with 17,022 medical institutions, which constituted 93.8% of medical institutions nationwide. Nearly all Taiwanese citizens

seek care through NHI (Chan et al., 2006). By the end of 2005, approximately 22.7 million individuals had been enrolled in Taiwan's NHI program - a coverage rate of 98% (Wu et al., 2012).

Unlike other healthcare systems which emphasise 'gatekeeper' roles, the insured individual in Taiwan can freely access any type of health provider, including clinics or medical centres, general practitioners or specialists, within the public or private sector. For people living in the mountainous areas and off-shore islands, the NHI provides extra funds for an integrated system to deliver primary care and some aspects of specialty care; co-payments are waived in those areas. There is usually no waiting line. It normally takes about two weeks to receive major surgery at the location of a patient's choice. One of the consequences of such easy accessibility to specialists is that the gatekeeper role of family physicians is relatively weak in Taiwan. Having limited gatekeeping means there is no check on whether Taiwanese people use specialty services appropriately. Indeed, the reported average number of outpatient department visits is 14 times per year per person in Taiwan which is higher than that in most of countries with well-established referral systems (Wu et al., 2010). To promote a referral system and to decrease non-essential outpatient visits, a 'non-referral co-payment policy' has been in operation since July 2005. If insured individuals directly access outpatient services in hospitals without a referral, they have to pay an extra 60% on top of the normal co-payment charge in local hospitals and 70% in regional hospitals and medical centres (Lu and Chiang, 2011). However, the out-of-pocket payment is still affordable with study results showing that this 'non-referral co-payment policy' fails to reduce the demand for health care. Taiwanese people still prefer to have direct access to larger-sized hospitals and

specialist cares (Chen et al., 2012).

All antidepressants can be prescribed by general practitioners or specialists to any insured patient. However, SSRIs and other new antidepressants are only reimbursed for officially approved indications. The Bureau of National Health Insurance sample and audit the claims for unnecessary use or fraudulent claims. Before the launch of NHI on 1 March 1995, the available antidepressants in Taiwan included amitriptyline, dothiepin, doxepin, imipramine, maprotiline, melitracen/flupentixol, fluoxetine, moclobemide and trazodone and two months after the launch, citalopram was introduced and reimbursed. By the end of 1997, clomipramine, fluvoxamine, paroxetine and sertraline had also been reimbursed. Venlafaxine has been reimbursed since 1 February 1999, mirtazapine since 1 April 2002, bupropion since 1 January 2003, milnacipran since 1 May 2004, escitalopram since 1 February 2005, and duloxetine since 1 December 2005 (Wu et al., 2012).

A study using a database of random sample of 145,304 adults provided by the National Health Insurance Research Database (NHIRD) in 2004 reported that one-year prevalence of antidepressant use in Taiwan was 4.3%. Among those with antidepressant use, 21.1% received them for neurotic depression, 17.6% for anxiety, 14.6% for MDD, 5.4% for depressive disorder not elsewhere classified and 2.6% for adjustment reactions. Regarding non-psychiatric medical conditions, the highest proportions of antidepressant use were for diseases of the genitourinary system, musculoskeletal system and connective tissue (Kuo et al., 2011). Antidepressants, like TCAs have an anticholinergic effect (Sawynok et al., 2001) that acts on bladder muscarinic receptors, which helps to relax the bladder muscle and contraction of the

detrusor, resulting in relief of the symptoms of urgency, frequency, and incontinence (Hunsballe and Djurhuus, 2001). There was also high use of antidepressants for diseases of the musculoskeletal system and connective tissue. These conditions may be variations of the diagnosis of fibromyalgia, which is characterised by the symptoms of widespread musculoskeletal pain, persistent fatigue, and non-refreshing sleep (Longley, 2006). Furthermore, a large proportion of antidepressant use in non-psychiatric disorders may be for their analgesic properties (Atkinson et al., 1999; Atkinson et al., 1998; Sawynok et al., 2001). Of diseases of the circulatory system, antidepressants are used most frequently for those with hypertension and hypertensive heart disease. Their use may be due to depression and anxiety being present in more than 50% of patients with hypertension, and combining an antidepressant with antihypertensive therapy seems to be of benefit (Vasiuk Iu et al., 2004). Antidepressants were also used for diseases of the nervous system and sense organs, including mononeuritis, vertiginous syndrome, and migraine for pain relief or vestibular balance (Adly et al., 1992; d'Amato et al., 1999). There are some hypotheses that using antidepressants may be beneficial in treating dizziness or vertigo (Blakley, 1999; Swartz and Longwell, 2005).

In another recent study examining all incident antidepressant use based on the NHIRD in Taiwan from 2000 to 2009 (Wu et al., 2012), 53.9% of subjects with mood disorders were found to be prescribed SSRIs, 19.3% TCAs, 17.4% trazodone, 11.3% other new agents (bupropion, duloxetine, milnacipran, mirtazapine and venlafaxine) and 4.6% moclobemide (MAOIs). For these cases of mood disorders, the average number of antidepressant prescriptions in the first-year of treatment ranged from 3.2 to 4.0 across antidepressant classes. In addition, the trend of incident antidepressant

use due to mood disorders in Taiwan was shown to increase from around four to five per 1,000 population from 2000-2005 and then to decrease to 3.5 per 1,000 population in 2009. There are a range of explanations for the decrease in incident use of antidepressants. The public concern about safety issues with antidepressant use may be important, as US data suggest (Libby et al., 2009; Olfson et al., 2008). Yet given the growing body of evidence of the effectiveness of antidepressants for chronic pain (Attal et al., 2006; Chou and Huffman, 2007; Chou et al., 2007; Evers et al., 2009; Hauser et al., 2010), the decline of antidepressant use for chronic pain was less obvious, remaining as the most common single non-psychiatric indication for antidepressant prescription in Taiwan (Wu et al., 2012).

1.4. Comorbidities of depression

The presence of comorbid chronic physical disorders is an important issue in the treatment of depression. Egede (2007) studied the one-year prevalence of depression in 10,500 patients with chronic diseases compared with healthy controls in the USA and found that those with chronic disease were almost three times more likely to be depressed (Egede, 2007). Compared to healthy controls, rates for depression were double in diabetes, hypertension, coronary artery disease and heart failure, and three times in end-stage renal failure, chronic obstructive pulmonary disease (COPD) and cerebrovascular disease (these comorbidities were also considered in the analyses of this thesis). In a WHO study of the one-year prevalence of depression among 245,400 patients in 60 countries, Moussavi et al. (2007) reported that those with two or more chronic physical health problems experienced a prevalence of depression of 23%, whereas in healthy controls the rate was only 3.2% (Moussavi et al., 2007). Similar

findings are also reported in the WHO World Mental Health Survey (Von Korff et al., 2009).

Physical illness has been shown to be a risk factor for the development of depression. Patten (2001) studied people who were free of depression at baseline in a large population-based cohort (n = 11,859); after two years, 3.5% of this group had developed MDD and physical illness was a risk factor (OR = 2.5, 95% CI: 1.3-4.6) (Patten, 2001). The risk was similar for a wide range of physical health problems, namely hypertension, asthma, arthritis and rheumatism, back pain, diabetes, heart disease and chronic bronchitis. In a Dutch cohort study of 4,664 participants who had never had depressive disorder, 2.7% of the population developed depression after one year and the presence of two out of three illnesses (migraine, respiratory problems or abdominal problems) predicted the later development of depressive disorder (Smit et al., 2004).

There are several ways in which a chronic physical health problem can cause depression. First, the number of different ailments a person experiences is directly proportional to the prevalence of depression. Dworkin and colleagues (1990) showed that patients with a single ailment had no increased risk of depression, those with two ailments had double the risk, and those with three or more had five times the risk (Dworkin et al., 1990). Second, chronic physical health problems carry the risk of disability and this can be very depressing. For example, researchers in the UK (Prince et al., 1997) demonstrated in a survey with over 65-year-old people (n = 654) that impairment, disability and handicap were strongly associated with depression; the adjusted odds ratio for depression in the most handicapped quartile compared with the

least was 24.2 (95% CI, 8.8-66.6). Ormel and colleagues (1997) showed similar findings in Holland (Ormel et al., 1997). Third, there are physical changes in some diseases that may underlie the development of depression, such as changes in the allostatic load. The term, allostasis, refers to the ability of the body to adapt to stressful conditions. Life stress, tissue damage and degenerative illness all increase allostatic load and can induce inflammatory changes which can then result in peripheral sensitisation of sensory neurons and activation of central pain pathways (Rittner et al., 2003). Taken together, there are a number of ways that depression and physical health problems interact with one another (Katon, 2003). For example, depression is associated with risk factors such as sedentary lifestyle, which are also risk factors for physical health problems. In addition, depression can be linked with poorer self-management of chronic physical health problems, which increases the burden of the disease. Moreover, the functional impairment associated with physical illness, as well as indirect pathophysiological factors (for example, increased cytokine levels or other inflammatory factors) may increase the risk of developing and worsening depression.

Depression can also precede a new episode of a physical health problem. Systematic reviews of 11 prospective cohort studies in healthy populations have shown that depression predicts later development of coronary heart disease (OR 1.18 to 5.4, median = 2.05) (Hemingway and Marmot, 1999; Nicholson et al., 2006). Nielsen and colleagues (1989) reported the occurrence of a depressive episode before an episode of myocardial infarction (Nielsen et al., 1989). Depression is also shown to be an independent risk factor in stroke (Everson et al., 1998; Larson et al., 2001; Ohira et al., 2001). The hypothesis is that the increases in proinflammatory cytokines and

adrenocortical reactivity in depression may lead to atherosclerosis, and with it increased risk for both stroke and coronary artery disease (Wichers and Maes, 2002). Besides, in prospective population-based cohort studies, depression has been shown to predict the later development of colorectal cancer (Kroenke et al., 2005), back pain (Larson et al., 2004) and multiple sclerosis (Grant et al., 1989), and although inconsistent, there is some evidence that depression may precede the onset of type 2 diabetes (Prince et al., 2007). Depression may also increase the likelihood of a person developing a physical disease by the immune changes including changes in immune cell classes with an increase in white cell counts and a relative increase in neutrophils, increases in measures of immune activation, and a suppression of mitogen-induced lymphocyte proliferation with a reduction in natural killer cells (Irwin, 1999).

It is believed that depression may lead to a shorter life expectancy (Evans et al., 2005) and, therefore, treatment might be expected to prolong life. For example, depressed patients were found to be three times more likely to be non-compliant with treatment recommendations than non-depressed patients, suggesting that there may be real advantages to treating depression among the physically ill (DiMatteo et al., 2000). Indeed, van Melle and colleagues (2004) reported a more than double greater risk of death with comorbid depression in people with heart disease (van Melle et al., 2004). However, the studies required to demonstrate the impact of treating depression on prolonging life in the physically ill have not been carried out because they would require long follow-up periods accompanied by prolonged treatment of depression with a control group not in receipt of such treatment. While randomised trials on the treatment of depression may report beneficial effects on outcome measures of depression, they often fail to show much effect on the physical illness including heart

disease (Berkman et al., 2003; Glassman et al., 2002) or diabetes (Katon et al., 2006; Williams et al., 2004). On the basis of a meta-analysis, Gilbody and colleagues (2006) conclude that while depression can be treated effectively by collaborative care there does not appear to be consistent evidence that such treatment improves physical outcomes (Gilbody et al., 2006).

There are other studies which have though found that treatment for depression has beneficial effects other than those on depression itself. Simon and colleagues (2005) showed improvements in social and emotional functioning, and disability, in a mixed group of people with chronic physical health problems (Simon et al., 2005); Mohr and colleagues (2007) demonstrated improvements in both disability and fatigue with CBT for depression in patients with multiple sclerosis (Mohr et al., 2007); Lin and colleagues (2003) showed that treatment of depression in patients with arthritis resulted in improved arthritis-related pain, functional outcomes, and better general health status and overall quality of life (Lin et al., 2003). Based on those studies, it seems that, in addition to reducing depressive symptoms, the treatment of depression is effective in reducing functional disability (Von Korff et al., 2009).

1.5. Costs of depression

Depression is among the most disabling illnesses in the world, and accounts for 9.6% of all years lived with disability (YLDs) (Vos et al., 2012). There is now widespread recognition of the significant burden that depression imposes on people and their carers, health services and communities throughout the world. Due to its high prevalence and treatment costs, its role as a key risk factor for suicide (Knapp and

Ilson, 2002), as well as its large impact on workplace productivity, depression places an enormous burden on both the healthcare system and the wider society.

Thomas and Morris (2003) estimated the total cost of depression (including costs for primary and secondary care, and indirect costs of lost working days (morbidity) and lost life years (mortality)) in adults in England in 2000 (Thomas and Morris, 2003). That study found that the direct treatment costs were £370 million, of which 84% was attributable to antidepressant medication; the indirect costs of depression were estimated to be far greater: Total morbidity costs were £8 billion and mortality costs were £562 million. More recently, a review was conducted to estimate mental health costs, including for depression, in England (McCrone et al., 2008). That indicated that the total cost of services for depression in England in 2007 was £1.7 billion, while lost employment increased the figures to £7.5 billion. By 2026, these figures were projected to be £3 billion and £12.2 billion, respectively. In contrast to the study by Thomas and Morris (2003) (Thomas and Morris, 2003), medication costs accounted for only 1% of total service costs while inpatient and outpatient care accounted for over 50% (psychiatric inpatients 10%; non-psychiatric inpatients 17%) (McCrone et al., 2008). In the USA, an earlier study showed that the total costs of depression in 1990 were estimated to be US$44 billion, with absenteeism and productivity costs accounting for US$24 billion (Greenberg et al., 1993). A Canadian study in 1998 estimated the total mental health burden to be $14.4 billion, placing mental health problems among the costliest conditions (Stephens and Joubert, 2001). One of the key findings from the cost-of-illness literature is that the indirect costs of depression far outweigh the health service costs. Thomas and Morris (2003) suggested that the effect on lost employment and productivity is 23 times larger than the costs for the health

service (Thomas and Morris, 2003). Based on UK labour market survey data, Almond and Healey (2003) estimated that individuals with self-reported depression/anxiety were three times more likely to be absent from work (equivalent to 15 days per year) than those without problems of depression/anxiety (Almond and Healey, 2003). A US study also suggested that depression is a major cause of reduced productivity while at work (Kessler et al., 2001). This reduced workplace productivity is unlikely to be adequately measured by absenteeism rates and further emphasises the 'hidden costs' of depression (Knapp, 2003). Other intangible costs of depression include the impact on the quality of life of people with depression and their carers. Indeed, the cost-of-illness calculations show that depression imposes a significant burden on people, family members, the healthcare system and on the broader economy. It is therefore important that efficient use of healthcare resources is made, to maximise health benefits for people with depression.

Cost of depression in Taiwan

The economic burden of depression depends on a number of factors, including its prevalence and treatment rates, as well as its debilitating nature. Over time, changes in any of these factors are likely to affect the estimated burden of illness (Greenberg et al., 2003). A study from nearly 20 years ago showed that the total cost of affective disorders (including bipolar disorder and major depression) in Taiwan in 1994 was US$1.4 billion, 25% of which were direct costs (Yeh et al., 1999). These figures were based on a bottom-up approach that surveyed more than 100 individuals and generated costs from these individual level data.

More recently, a top-down approach was used to measure the burden of depression among adults over the age of 15 years in Taiwan for the three years 2000-2002 (Chan et al., 2006). Medical claims were characterised in claims data as depression-related using International Classification of Diseases, Ninth Revision codes (ICD-9) 296.00-296.99 (affective psychoses, including: manic disorders, major depressive disorders, bipolar affective disorders, atypical manic or depressive disorders, other manic-depressive psychosis, unspecified or other specified affective psychoses), 311 (depressive disorders, not elsewhere classified), and 300.4 (neurotic depression). The prevalence data for depression and rates of depression were taken from an estimation by the Social and Economic Burden of Depression study in the Asia-Pacific Region (Sartorius, 2004), with participants including Taiwan, China, the Philippines, Singapore, Thailand, Malaysia, and Pakistan. The results showed that in Taiwan, total national health care expenditures in 2000-2002 were around US$9 billion for each year. The direct medical costs of depression in 2000, 2001, and 2002 were estimated to be US$93 million, US$117 million, and US$140 million, respectively. Medication use was found to be an important contributor to health care expenditures for depression in Taiwan, accounting for 49.0%, 48.3%, and 48.4% of costs in 2000-2002 (Chan et al., 2006). Together with the studies showing that antidepressant use in Taiwan doubled from 1997 to 2004 (Chien et al., 2007a) as well as the increase in the annual treated incidence of MDD from 1.89 per 1000 in 1997 to 2.58 per 1000 in 2003 (Chien et al., 2007b), the burden of depression treatment in Taiwan has been increasing and the economic aspects of depression treatment need to be assessed.

1.6. Economic evaluation

Economic evaluation

In health care, evidence based decision-making is becoming an established part of modern clinical practice. It is increasingly common in many countries for evidence on the clinical effectiveness of interventions to be accompanied by an economic evaluation, in which the costs of the treatments are analysed alongside the effects. There are reasons why economic evaluations are increasingly carried out alongside clinical evaluations in health care. For example, in the UK, a report by the King's Fund estimated that mental health services have received a large increase in funding in recent years (McCrone et al., 2008) and yet resources remain inherently limited. At any one time there are a maximum number of mental health professionals working in the system, a limited number of inpatient beds available, a restricted budget for psychotropic medication and as yet no evidence whatsoever of any limit to demand. The benefit of the alternative foregone is what economists call 'opportunity cost' (Rutherford, 1995). Every decision to fund a service or treat a patient in a resource constrained healthcare system has to be associated with a loss elsewhere and it is this loss, or opportunity cost, that is a key focus of economics.

Economic evaluation is concerned with the efficient allocation of available resources between alternative uses (Rutherford, 1995). As the people, equipment, and facilities of health care are scarce, economics can provide a useful framework in which the possible alternative uses of the available resources can be compared. In this way, economic evaluation seeks to maximise outcomes from available resources. There are

a range of approaches that can be taken to conducting an economic evaluation. These related elements are explored in Chapter 3, but are first briefly explained below.

Comparison group

A principle of economic evaluation is that it should be comparative, since it is concerned with the allocation of scarce resources that could be used for a number of different purposes. Consequently, all economic evaluations should involve the comparison of at least two groups. The choice of the comparator, e.g. treatment as usual or a head-to-head comparison is very important since it will influence the size of the difference in costs and effects. In an economic evaluation, the ideal comparator should be the next best alternative (Gold et al., 1996b).

Perspective

The evaluation must establish the perspective that it will take and determine which costs will be included and which costs excluded. An evaluation can take a narrow perspective, including only the cost of the intervention or programme under evaluation, or a wide cost perspective in which the costs of the programme and other health care cost, family costs and resources consumed in other sectors are included (Drummond et al., 1997; Gold et al., 1996a). For instance, an evaluation of a health care programme taking a wide perspective could include health care costs alongside resources consumed in other sectors such as social services, the criminal justice sector and education. A societal perspective would also include out-of-pocket costs to families, such as the costs of transport to hospital and the costs of time taken by

family and friends as informal carers, and time taken off work due to the ailment.

Costs

An economic evaluation needs good quality evidence on the costs of the resources used by the treatment and comparator groups. The perspective will help guide the researcher in identifying which costs should be included. It may also be necessary to review the literature on the services used being evaluated and to discuss relevant services with service users and clinicians. There exist a number of approaches for measuring these resources including service use questionnaires and the examination of patient records. Once information on service use has been collected, unit costs are applied to each piece of service use information and total costs are calculated. In economic evaluations, it is common to collect information on use of all resources, including apparently unrelated resources, rather than just resources that are associated with the health problem being evaluated (Glick et al., 2007).

Outcomes

The choice of effectiveness or outcome measure is directly related to the method of economic evaluation chosen and these issues are further explored later. Disease- or condition-specific outcomes are often used in evaluations of healthcare programmes. However, in many cases the consequences of an intervention are multi-dimensional and it is difficult to capture these complexities in a single outcome measure (Brazier et al., 2007a). Therefore, multiple secondary outcome measures are often used besides the primary outcome measure in economic evaluations. Furthermore, economists have

another concern: economic evaluations should aid decision-makers who want to maximise the healthcare benefits from available budgets across different disease areas. Thus, the measure of outcomes should ideally allow the comparison of treatments across a range of diseases and conditions, which is very difficult if every disease area uses a different outcome measure. This has led to the development of generic outcome measure such as the quality-adjusted life-year (QALY). The QALY approach provides a single index that combines information both on the length and quality of life (Brazier et al., 2007a). It is though evident that QALYs may not be able to capture all the benefits of a healthcare intervention (Knapp, 2007). For example, an improvement in the health of a patient may impact on the health of their caregiver as well. While some of these impacts can be captured in the analysis, it would not always be possible to capture all benefits of an intervention in a single index. A fuller discussion of the use of QALYs will be provided in Chapter 5.

Study design

Study design is the means by which data on the costs and outcomes of the two courses of action are collected. Data can be collected within a range of study designs and ideally data should be collected in a way that minimises bias. Possible study designs include randomised controlled trials, observational designs and decision modelling. These designs are examined in detail in Chapter 3.

Method of economic evaluation

Data on the costs and effects of the treatment and comparator group are formally

compared in a number of ways. Different methods of economic evaluation vary in the valuation of outcomes. The most commonly employed methods are discussed below and summarised in Table 1.1.

Table 1.1 Methods of economic evaluation

Method of economic evaluation	Costs	Outcomes
Cost-effectiveness analysis	Money	Single disease-specific measure
Cost-utility analysis	Money	Utility based outcome (e.g. QALY)
Cost-consequences analysis	Money	Range of disease-specific measures
Cost-minimisation analysis	Money	None; assumed equal
Cost-benefit analysis	Money	Money

In a *cost-effectiveness analysis,* costs are considered alongside disease-specific outcomes. A cost-effectiveness analysis can be undertaken using the disease specific outcome measures that are collected as measures of effectiveness for the clinical evaluation and so the results may be more easily presented to clinicians and/or decision-makers. In health care evaluations, the incremental costs and effects of the treatment over the comparator are determined and used as the basis for analysis. The incremental cost-effectiveness ratio (ICER) is the ratio of differences in costs between intervention and comparison groups and the differences in outcomes. This kind of economic evaluation is limited by the narrow focus on a single measure of outcome. There can be difficulties in evaluating treatments that impact on more than one outcome and problems in attempting to compare the results of evaluations across disease groups where outcomes have been measured using different measures. Cost-effectiveness analysis does though remain a widely used technique especially when a decision-maker is considering a limited range of options within a given field (Drummond et al., 1997).

A *cost-utility analysis* is similar to a cost-effectiveness analysis but it considers costs alongside a utility based outcome measure, usually QALYs. The advantage of cost utility analysis is that the results can be compared across different disease areas, although criticisms of the use of generic measures to generate QALYs in mental health populations should be borne in mind when designing or appraising a cost-utility analysis (Chisholm et al., 1997).

In a *cost-consequences analysis*, costs are presented alongside a range of outcomes. Costs and outcomes are not formally combined in this analysis. Cost-consequences analysis is a useful approach when little is known on the subject, or when it is difficult to identify an adequate primary outcome measure for a cost-effectiveness analysis.

Outcomes are assumed to be, or have been proven to be, equal in a *cost-minimisation analysis*. Since outcomes are the same, the decision is made on the relative costs of the intervention and comparator. Cost-minimisation analysis is rarely appropriate because there is almost always statistical uncertainty around any measurement of outcomes (Briggs and O'Brien, 2001).

In a *cost-benefit analysis*, outcomes are translated into monetary values so that the analysis is able to make a direct comparison of the outcomes and costs. The advantage of cost-benefit analysis is that it allows the comparison of different interventions or programmes not only across health care, but also other areas, making it broader in scope and potential useful (Sugden and Williams, 1978). The main disadvantage is the difficulty of assigning monetary outcomes to outcome measures.

1.7. Structure of the thesis

In this Chapter, the background to depressive disorders including its prevalence, course, pharmacological treatments and physical comorbidities has been examined. Some information relating specifically to Taiwan has also been provided. A range of methods of economic evaluations have been summarised.

The second chapter contains a systematic review of published economic evaluations in antidepressant treatments and aims to identify existing methods of economic evaluations in this area and any gaps in the current knowledge. Using the results of the review, useful evaluation approaches for subsequent analyses in this thesis have been identified.

Chapters 3 and 5 are a critical appraisal for methods of economic evaluation, study designs, and outcome measures. In Chapter 3, the study design and methods of economic evaluations are discussed. In Chapter 5, appropriate outcome measures for cost-effectiveness analysis for antidepressant treatments are considered.

Chapters 4, 6 and 7 report the results of the application of these methods. In Chapter 4, the results of an economic evaluation of treatment costs for patients with depression and the associated factors including comorbid cardiovascular diseases and pain disorders are reported. In Chapter 6, an economic evaluation involving impacts of initial treatment outcomes on service use and costs within the following three years is reported. In Chapter 7, the results of a cost effectiveness (utility) analysis of antidepressants treatments with a particular focus on comorbid cardiovascular

diseases are reported.

Finally, Chapter 8 summarises major findings from previous chapters and discusses limitations, strengths, and implications of studies in this thesis.

Chapter 2. Systematic review of economic evaluations of antidepressant treatments: evidence from database analyses and prospective studies

This chapter reports results from a systematic review of economic evaluations of antidepressant treatments in patients with depression. The focus is on comparisons between prospective studies and database analyses. The specific purposes are: first, to inform the methodological approach taken in the subsequent evaluation and second, to place the results in context. In terms of methods, the review provides information on the approach needed for the most appropriate outcome measure for an evaluation in that patient group. The review can also help deciding on study design and follow-up period.

2.1. Introduction

An economic evaluation should be preceded by a review of the published literature. The investigator designing the economic evaluation may then use the information gathered in the review and measure costs in a similar manner, or choose to use the same outcome measure so as to make useful comparisons between the results of the evaluation and existing evidence. Furthermore, the review helps to identify gaps in the knowledge in the existing literature. The investigator might therefore use a specific method to explore a particular question.

The prospect of making meaningful comparisons and of identifying gaps in the existing knowledge is linked to the above-mentioned second purpose of a systematic review, i.e. to place the results of the evaluation once completed in the context of what

is already known on the subject. It is also important to note that economic evaluations are particularly context specific. For example, studies carried out in the USA may not be very informative for study design in Taiwan or the UK. Therefore, a systematic review may provide an opportunity to compare results from different settings and inform study designs in a specific setting.

In Chapter 1, an initial exploration of the literature suggested that depression is a severe and pervasive disorder. Unipolar depressive disorder was the fourth leading cause of burden among all diseases in 2002 and its impact will continue to grow in future decades (Mathers and Loncar, 2006). Given its marked personal, social and economic impacts, depressive disorder creates significant demands on individuals, health service providers and society as a whole. Although pharmacological, psychological and case management interventions are all recommended, antidepressant drugs remain the mainstay of treatment for depression for most people in contact with healthcare services (NICE, 2009), which may be partly due to a shortage of therapists in some countries. The last 20 years have seen dramatic changes in antidepressant prescription patterns. Initially, there was an increase in the use of the selective serotonin reuptake inhibitors (SSRIs), which resulted in a progressive rise in total drug expenditures for antidepressants (Barbui et al., 2001; Eccles et al., 1999). Subsequently, other novel antidepressant agents with different pharmacological mechanisms entered the market. Given the range of choices, clinicians must decide about which is the most appropriate intervention for their patients (Simon et al., 1996).

To this end, knowledge regarding the relative cost-effectiveness of individual

antidepressants is important, especially for policy makers. In contrast to the substantial evidence on efficacy and tolerability of antidepressant treatments from randomised controlled trials (RCTs), data specifically addressing cost-effectiveness in real-world settings are scarce (Brunoni et al., 2009; Montgomery et al., 2005). At the same time, the clinical meaning of the statistical differences in the efficacy or tolerability in RCTs remains uncertain (Cipriani et al., 2005; Cipriani et al., 2009) because study settings and populations of RCTs are principally protocol-driven and operate strict inclusion and exclusion criteria. This limited level of external validity makes it difficult to generalise results to the context of routine medical practice.

Given the gap in knowledge from real-world settings, database analyses using information from actual clinical practice might provide valuable insights into depression treatments for more heterogeneous populations to complement evidence from controlled trials. These studies can utilise large administrative databases such as medical claims that capture patients' resource utilisation. However, the methodological approaches employed in economic evaluations using database analyses have been diverse and there have been few reviews of their strengths and limitations. The aim of this review is to systematically assess methodological approaches used in retrospective database analyses of the cost-effectiveness of antidepressant agents in depression treatment. For comparative purposes, economic evaluations from prospective studies are reviewed as well to illustrate differences in methodological approaches.

2.2. Methods

Search strategy

Studies were identified through a Medline, PsycInfo, and Embase electronic search performed with no limits in language but with limits to human studies ranging from the year 1999 to 3 September 2010. Three sets of keywords included: cost or cost effectiveness or cost benefit or cost utility or cost consequence or comparative effectiveness; antidepressant; depression or depress$ or major depressive disorder. Reference lists of included papers and previous reviews were hand-searched for published reports missed by the electronic search. Unpublished studies/grey literature were not included in this review.

Inclusion criteria

A structured form was designed to record the eligibility of the initially identified papers from the electronic search for inclusion in the final review. All located papers were first screened by reviewing the titles. The review was initially performed by the student with a subsequent check by the first supervisor to identify potentially relevant studies. When it was not clear whether a particular study should be included, the full paper was reviewed to ensure eligibility. No limitation on the age of study subjects was applied. Articles had to meet the following criteria to be included in the review:

- Comparative analysis of alternative antidepressant treatments (or antidepressant versus placebo) for depressive disorders.
- Studies undertaken based on a database analysis, an RCT (either

conventional or pragmatic), or a naturalistic observational study.

- Economic evaluations, including cost analysis, cost-effectiveness analysis, cost-benefit analysis, cost-utility analysis, and cost-consequence analysis.
- Published studies in peer-reviewed journals.

Data extraction

A structured form was used for the extraction of information on the year of publication, study design, study perspective, length of follow-up, country and setting of the study, antidepressants compared, sample size, study inclusion/exclusion criteria (including patient age, diagnosis, and certain comorbidities), measurements of baseline disease severity (e.g., number of comorbid physical or mental disorders, emergency room visits, or hospitalisation before the index date), methods of economic evaluation, and funding sources. Additional information on study results was extracted with respect to measures of costs and outcomes as well as cost-effectiveness.

Analysis

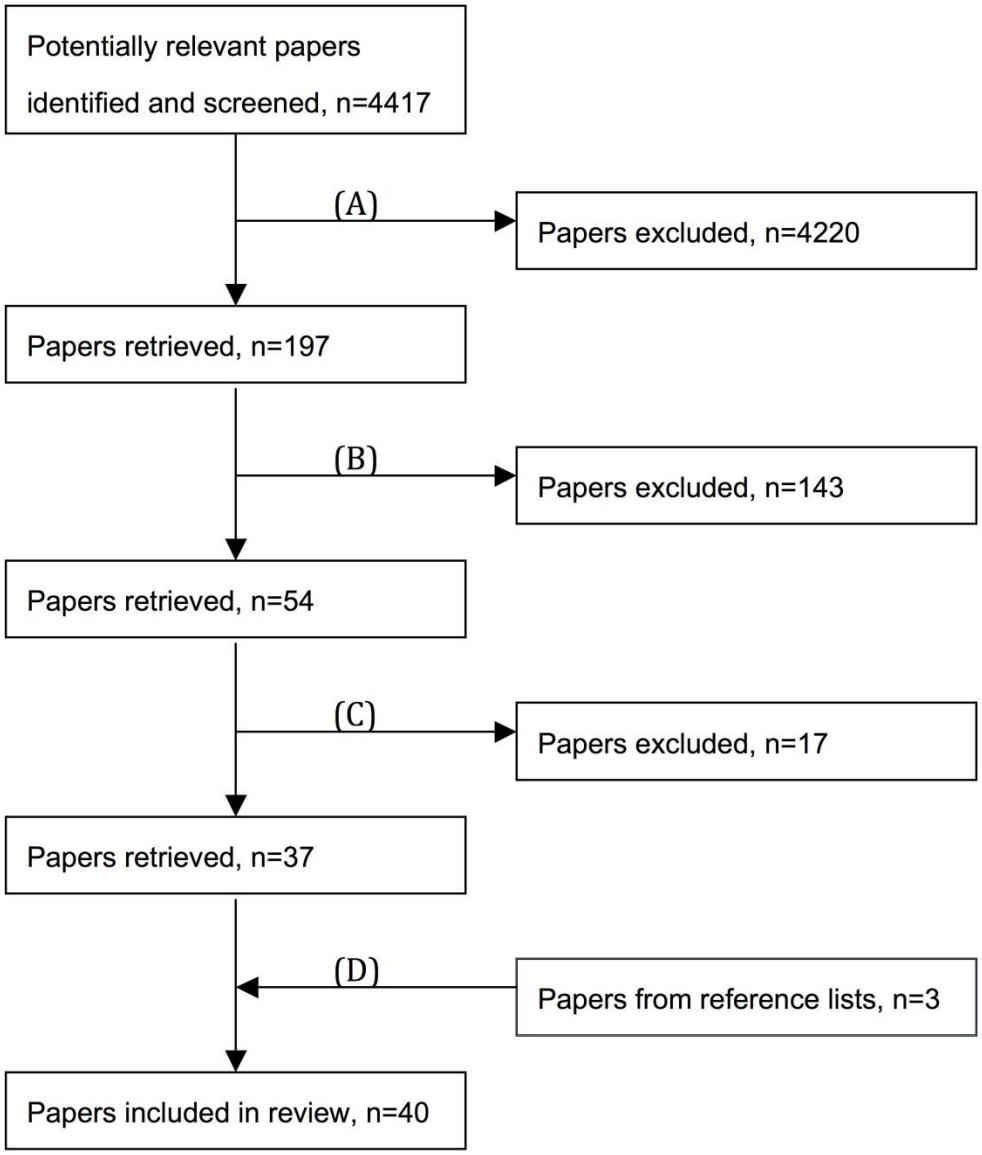
The outcomes of interest included total healthcare costs, healthcare costs plus indirect costs, compliance with treatment, hospitalisation rates, and change in clinical symptoms/or quality of life measurements. Results were compared and classified according to study designs, i.e., retrospective database analyses, conventional RCTs, and pragmatic RCTs plus naturalistic observational studies. A key difference between pragmatic RCTs and conventional ones is that the former aim to keep exclusion

criteria to a minimum and may often recruit a group of patients with more heterogeneous features - a common feature of patients with mental disorders in routine practice settings - than those included in conventional RCTs which usually focus on narrower diagnostic groups.

2.3. Results

A breakdown of inclusion and exclusion is given in the Quality of Reporting on Meta-analyses standards (QUOROM) diagram (Moher et al., 1999) in Figure 2.1.

Figure 2.1. QUOROM flow diagram of articles included in the systematic review



As seen in Figure 2.1, the electronic search yielded 4417 studies but an initial review

of titles led to the exclusion of 4220 because (A) they did not focus on depression treatment, they were not comparative analyses of alternative antidepressants (or antidepressant versus placebo), or they did not include costs. For the remaining 197, the abstracts were reviewed to identify potentially relevant papers and a further 143 excluded mainly because (B) on closer examination they were found not to be economic evaluations, or they were not based on one of the designated study designs to be covered by this review. For the remaining 54, the full papers were reviewed and a further 17 excluded because (C) they were not economic evaluations based on a database analyses, an RCT, or a naturalistic observational study. Then, (D) reference lists of included papers and previous reviews were hand-searched and another three studies were identified, thus 40 papers were included in the final review: 28 retrospective database analyses and 12 prospective studies.

In assessing the quality of economic evaluations of mental health interventions in a previous review, Evers et al. (1997) identified a number of common weaknesses in study design, including short follow-up periods and lack of justification of sample sizes (Evers et al., 1997). In a more recent review of cost-effectiveness of treatments for depression, Barrett et al. (2005) highlighted specific difficulties in synthesising evidence from various economic evaluations because of the use of different outcome scales and different perspectives across studies (Barrett et al., 2005). This is often a concern because there has not been a universal outcome scale used for economic evaluations even for the same disease entity, e.g., depressive disorders. This is partly attributable to mental disorders having impacts on multiple dimensions, but even for the same dimensions there are often a number of possible outcome measures to use. The key characteristics of the included papers are summarised in Tables 2.1 and 2.2.

Follow-up periods for five RCTs were less than or equal to 24 weeks. Fifteen studies lasted for six months and the remaining 19 studies for at least 12 months. The effectiveness of the treatments was recorded using nearly 20 different outcome measures, including treatment persistence and hospitalisation. Only four studies used a primary outcome measure of quality of life. Most studies used process or service outcomes instead of clinical outcomes. While indirect costs including productivity losses may occur as a result of impaired working ability, only 16 papers considered a broad perspective of costs and the remainder (n=24) considered only costs to healthcare systems. Two of the included studies were carried out in multinational settings; another eight studies were from individual European countries, one from India, and the remainder (n=29) from North America (Tables 2.1 and 2.2).

Findings from retrospective database analyses

Characteristics and methodological approaches of studies based on database analyses

Most included database analyses were carried out in the United States or Canada, with one exception which used primary care data from the United Kingdom (Wade et al., 2010) (Table 2.1). The study populations were mostly adults aged 18 years or above (some of them recruited only working-age adults), with the exception of three studies focusing on elderly populations (Tournier et al., 2009; Wu et al., 2008a; Wu et al., 2008b). The majority of these analyses adopted a similar methodology, based on the identification of patients who had a paid insurance claim that indicated a diagnosis of a depressive disorder and treatment with antidepressants. Diagnoses of a depressive

disorder included major depressive disorder and dysthymic disorder (or neurotic depression) in most studies; several studies recruited only subjects with major depressive disorder and one study focused exclusively on subjects with severe depression (Wade et al., 2010). Another three studies recruited subjects with a diagnosis of either depression or anxiety disorder (Sheehan et al., 2004; Sheehan et al., 2005; Sheehan et al., 2008) while the others also included subjects with a diagnosis of bipolar depression (Griffiths et al., 1999; Sullivan et al., 2000) or bipolar disorder (Ackerman et al., 2002). In these studies, the impact of 'pure' depression would be difficult to estimate due to the recruit of mixed populations.

The most often used proxies for baseline clinical characteristics were number of concomitant disease states and baseline healthcare utilisation, e.g. the number of emergency room visits or hospitalisations before the index date. An intention-to-treat (ITT) principle was applied in most cases and patients were assigned to a drug cohort on the basis of their initial prescription, with resource utilisation data over a specified study period after the first prescription analysed and compared between drug cohorts. Compared to an RCT, more sophisticated statistical methods would be needed in database analyses to address the likely systematic differences in the baseline characteristics across subjects from different drug cohorts due to the non-random assignment of treatments. The most commonly used methods in the reviewed studies to account for such differences have been regression modelling. More recently, methods based on propensity scores have been proposed to reduce or eliminate the effects of confounding in observational studies (Austin, 2011) but only one study was found to use a propensity score-adjusted method (Wade et al., 2010) in this systematic review. The propensity score was defined to be the probability of treatment

assignment conditional on observed baseline characteristics. Conditional on the propensity score, the distribution of measured baseline covariates was similar between subjects receiving different interventions. Therefore, under certain assumptions, conditioning on the propensity score allows one to obtain unbiased estimates of average treatment effects. Four different propensity score methods are often used for removing the effects of confounding when estimating the effects of treatment on outcomes: propensity score matching, stratification (or sub-classification) on the propensity score, inverse probability of treatment weighting using the propensity score, and covariate adjustment using the propensity score (Austin and Mamdani, 2006; Austin, 2011).

A healthcare perspective for costing was adopted in all studies, although some of them also took into consideration out-of-pocket payments by patients including copayments, coinsurance, and/or deductibles (Table 2.1). Among the 28 database studies, seven were cost analyses, and the remaining 21 were cost-consequence analyses where costs were reported alongside a range of outcome measures. Treatment persistence, odds of hospitalisation, and guideline adherence were the most frequently used outcome measures (although from an economic point of view service use such as inpatient stays is more correctly seen as an input rather than an outcome). Study periods ranged from six to 24 months. Of the 28 included studies, 23 were funded by pharmaceutical companies. In one of the two studies funded by government agencies (Ackerman et al., 2002; Tournier et al., 2009), the authors provided consultancy services to the pharmaceutical industry (Tournier et al., 2009). In a further two studies in which funding sources were not stated, the authors either provided consultancy services to the pharmaceutical industry (Sheehan et al., 2005) or were employees of the

pharmaceutical companies (Poret et al., 2001). Only one study declared no conflicts of interest (Chung, 2005) (Table 2.1). It is thus important to interpret these results taking into consideration competing interests as it is reasonable that pharmaceutical companies may tend to publish favourable results.

Economic evaluations comparing antidepressants using database designs

Four studies were primarily designed to compare escitalopram with other antidepressants. Escitalopram was shown to have better treatment persistence and lower total healthcare costs compared to other SSRI/SNRIs in a large sample of adult patients (Wu et al., 2008b; Wu et al., 2009). In another study which included severely depressed adult patients, there were significantly fewer hospitalisations per patient in the escitalopram versus venlafaxine or generic SSRI groups and the total annual healthcare expenditure per patient was lower in the escitalopram group compared to venlafaxine but similar between escitalopram and generic SSRIs (Wade et al., 2010). Escitalopram was shown to have better treatment persistence, a lower hospitalisation rate, and lower total healthcare costs than citalopram in a geriatric population (Wu et al., 2008a). These studies were funded by the same pharmaceutical company and escitalopram was the antidepressant of interest in all of them.

In a comparison between venlafaxine XR (a form of extended-release venlafaxine) and SSRIs (citalopram, fluoxetine, paroxetine, and sertraline), better treatment persistence was found for the former but total direct medical costs were comparable (Monfared et al., 2006). Patients prescribed with venlafaxine were reported to have lower odds of hospitalisation for non-mental-health reasons than those prescribed with

SSRIs, while total healthcare costs were similar between the two groups. However, some other studies failed to demonstrate differences in treatment persistence between venlafaxine XR and SSRIs (Wan et al., 2002a, b). Two cost analyses with similar study designs revealed that total medical expenditures were generally similar among patients receiving venlafaxine, SSRIs, or TCAs as a second-line therapy for depression (Griffiths et al., 1999; Sullivan et al., 2000). Another study comparing healthcare costs of patients who switched antidepressants versus those who did not found that switchers had higher total healthcare costs than non-switchers. For patients switching from an SSRI to venlafaxine, mean medical cost reductions offset higher pharmacy costs of venlafaxine after the switch, and for those switching from venlafaxine to an SSRI, mean medical and pharmacy costs declined after the switch (Khandker et al., 2008). Each of the above studies was again funded by the same pharmaceutical company. Another study, funded by a government agency (Tournier et al., 2009), showed similar treatment persistence and costs for medical service utilisation and psychiatric hospitalisation between venlafaxine (n=1937) and SSRIs (n=8186).

There were 12 database analyses included in the review that used TCAs as a comparator treatment. One study showed that patients treated with SSRIs were more likely to meet treatment duration recommendations than those treated with TCAs, and among compliant patients the mean total healthcare costs were lower for SSRIs (Baker et al., 2001). SSRIs were shown in a bivariate probit model to reduce patients discontinuing pharmacotherapy compared to TCAs, but total healthcare charges were similar between the two groups (Dobrez et al., 2000). Despite comparable total healthcare expenditures between treatment groups, SSRI users were shown to have

higher depression-related service expenditures but lower non-depression-related service expenditures than TCA users (Sullivan et al., 2000). It was further revealed by Baker et al. (Baker et al., 2001) that among patients compliant with treatment duration recommendations, non-depression-related costs were lower for those prescribed SSRIs than for those prescribed TCAs (Baker et al., 2001). There was also evidence suggesting that SSRIs reduced overall outpatient visits and the use of other prescription drugs, but resulted in increased utilisation of services for depression, which then cancelled out the potential cost advantage of SSRIs over TCAs (Chung, 2005). Although speculative, SSRIs were shown to be associated with reduced non-depression-related expenditures which may be due to lower use of other prescriptions for depression-related somatic symptoms and better engagement in depression treatment.

Compared to patients prescribed TCAs, fluoxetine patients were shown to be half as likely to be hospitalised (Croghan et al., 2000) and to have lower total healthcare costs (McCombs et al., 1999). Similarly, citalopram was reported to result in better treatment persistence and lower total healthcare costs than the TCA amitriptyline (Sclar et al., 1999). Lower nursing home and other costs were found in a comparison of sertraline versus TCAs (McCombs et al., 1999), but another study revealed a similar likelihood of hospitalisation for patients initially prescribed sertraline and TCAs (Croghan et al., 2000). In a study comparing bupropion SR (noradrenaline dopamine reuptake inhibitor) with other antidepressants, total healthcare costs were shown to be lower for patients treated with bupropion SR than for those treated with TCAs and in comparison with bupropion SR, patients initiating therapy with sertraline had significantly higher mental health payments (Poret et al., 2001).

Turning to comparisons between different SSRIs, the results were largely mixed. A head-to-head comparison favoured sertraline in having lower depression-related costs than citalopram (McLaughlin et al., 2004), but a contradictory finding emerged in another study favouring citalopram in having lower total and depression-related healthcare costs (Sclar et al., 1999). Likewise, sertraline was shown to have lower total and depression-related costs than fluoxetine in one study (Berndt et al., 2000), but in another study, fluoxetine was shown to have better treatment persistence than sertraline and paroxetine while total healthcare costs were similar between antidepressant groups (Polsky et al., 2002; Russell et al., 1999) as were total healthcare costs in another study (Crown et al., 2001). One study examined the 'cost-persistence ratio' in a comparison of SSRIs (Tournier et al., 2009). Persistence was considered as an indicator of effectiveness because premature discontinuation is often a consequence of treatment failure related to adverse effects, or absence of clinical benefits; non-persistence was defined as treatment duration of less than 180 days in a follow-up period of 12 months. Paroxetine was shown to have the most favourable results (lower cost-persistence ratio), but fluoxetine was considered the best choice in terms of *incremental* cost-persistence ratio (the difference in costs between the two treatments divided by the difference in outcomes - frequency of persistent treatments - between the two treatments).

Beyond comparisons between different antidepressants, one study of patients with major depressive disorder revealed significantly higher total healthcare costs for those not receiving any initial psychotropic medications compared to either those treated with TCAs or SSRIs (Optenberg et al., 2002). Further research compared the same

antidepressant compounds with different release patterns. Paroxetine CR was shown to have better treatment persistence and lower medical costs relative to paroxetine immediate release (IR) (Sheehan et al., 2004). Elsewhere, compared to other SSRIs (including paroxetine IR) as a group, paroxetine CR was also shown to have lower medical costs (Sheehan et al., 2005). Several studies principally focused on hospital charges (Ackerman et al., 2002; Croghan et al., 2000). In one of them, initial use of heterocyclic agents was shown to be associated with higher hospital charges than monoamine oxidase inhibitors (MAOIs), SSRIs and venlafaxine, despite the major cost drivers being other more expensive procedures, e.g. electro-convulsive therapy, rather than choices of antidepressant treatments (Ackerman et al., 2002). The remaining study defined all antidepressants launched after 2002 as 'third-generation antidepressants' (bupropion XL, duloxetine, venlafaxine XR, escitalopram, paroxetine CR) and reported that newer generation antidepressants were associated with lower total medical costs (excluding pharmacy costs), lower odds of all-cause hospitalisation, and better adherence (Sheehan et al., 2008).

Table 2.1. Characteristics of included papers of database analyses

Study	Interventions	Country	Depression diagnoses	Cost perspective	Study period (months)	Outcomes	Economic evaluation	Sponsor
Wade et al. (2010) >= 18Y/O	Escitalopram (n=323), venlafaxine (n=215), generic SSRIs (n=1947)	UK	Severe depression according to GPRD	Health care	12	Hospitalizations per patient	Cost-consequences	H.Lundbeck A/S
Wu et al. (2009) >=18Y/O	Escitalopram (n=10465), SSRI/SNRIs (n=28310)	USA	ICD-9-CM: 296.2, 296.3	Health care	6	Discontinuation, switching, time from discontinuation to the first ER visit	Cost-consequences	Forest Research Institute, Inc.
Tournier et al. (2009) >=66Y/O	Citalopram (n=2321), fluoxetine (n=360), fluvoxamine (n=883), paroxetine (n=2353), sertraline (n=2269), nefazodone (n=360), trazodone (n=2342), venlafaxine (n=1937)	Canada	Not stated	Health care+out of pocket payments	12	Treatment non-persistence	Cost-consequences	Government
Wu et al. (2008a) >=65Y/O	Escitalopram (n=459), SSRI/SNRIs (n=1517)	USA	ICD-9-CM: 296.2, 296.3	Health care	6	Discontinuation, switching rate, hospitalization rate	Cost-consequences	Forest Laboratories, Inc.
Wu et al.	Escitalopram (n=459), citalopram	USA	ICD-9-CM: 296.2,	Health care	6	Discontinuation, switching rate,	Cost-consequences	Forest

(2008b) >=65Y/O	(n=232)		296.3			hospitalization rate		Laboratories, Inc.
Khandker et al. (2008) >=18Y/O	Venlafaxine (n=5297), SSRIs (citalopram, fluoxetine, paroxetine, sertraline, n=43653)	USA	ICD-9-CM 296.2, 296.3, 300.4, 311	Health care	12		Cost-analysis	Wyeth Research
Sheehan et al. (2008) >=18Y/O	3rd generation (n=83800), 2nd generation (n=161166), 1st generation ADs (n=21699)	USA	ICD-9-CM 296.2, 296.3, 300.4, 311 300.01,300.21, 300.22, 300.23,300.3, 309.81, 308.3, 300.02, 300.00	Health care	6	Adherence rate, hospitalization rate	Cost-consequences	GlaxoSmith Kline
Monfared et al. (2006) >=18Y/O	Venlafaxine XR (n=3150), SSRIs (citalopram, fluoxetine, paroxetine, sertraline, n=13994)	Canada	ICD-9-CM 296.2, 296.3, 300.4, 309.0, 309.1, 311	Health care + out of pocket payments	12	Treatment persistence, compliance rate	Cost-consequences	Wyeth Pharmaceuticals
Sheehan et al. (2005) >=18Y/O	Paroxetine CR (n=10072), sertraline (n=40539), paroxetine (n=30522), citalopram (n=29722), fluoxetine (n=20693), escitalopram (n=14527)	USA	ICD-9-CM 296.2, 296.3, 300.4, 311 300.01,300.21, 300.22, 300.23,300.3, 309.81, 308.3, 300.02, 300.00,	Health care	6		Cost-analysis	None declared

			293.89					
Chung (2005) No age limitations	SSRIs (n=771), TCAs (n=171)*	USA	ICD-9 codes of 296, 300(accompanied by CCC69), 309(accompanied by CCC72), and 311	Health care + out of pocket payments	**13.2		Cost-analysis	None declared
Sheehan et al. (2004) >=18 Y/O	Paroxetine CR (n=1275), paroxetine IR (n=2550)	USA	ICD-9-CM 296.2, 296.3, 300.4, 311 300.01,300.21	Health care	6	Time to discontinuation	Cost-consequences	GlaxoSmith Kline
McLaughlin et al. (2004) >=18 Y/O	Citalopram (n=3175), sertraline (n=15222)	USA	ICD-9-CM 296.2, 296.3, 300.4, 311	Health care	6	Treatment persistence, use of other ADs	Cost-consequences	Pfizer Inc.
Ackerman et al. (2002) No age limitations	TCAs (n= 124 hospitalizations), MAOIs (n=9), atypicals (trazodone, nefazodone, bupropion, n=211), SSRIs (n=798), venlafaxine (n=119), multiple medications (n=437)	USA	ICD-9 296, 311	Health care (only hospital charges)	During hospitalizations		Cost-analysis	Government
Optenberg	SSRIs (n=697), TCAs (n=311), no	USA	ICD-9-CM 296.2	Health care	12	Hospitalisation (%), inpatient	Cost-consequences	GlaxoSmith

et al. (2002)	medications (n=811)					days		Kline
>=18 Y/O								
Wan et al. (2002a)	Venlafaxine (including venlafaxine XR, n=468), SSRIs (n=8625)	USA	ICD-9-CM 296.2, 296.3, 300.4, 309.0, 309.1, 311	Health care + out of pocket payments	6	Adherence, odds of hospitalisation	Cost-consequences	Wyeth-Ayerst Research
>=18Y/O								
Wan et al. (2002b)	Venlafaxine (including venlafaxine XR, n=353), SSRIs (n=7330)	USA	ICD-9-CM 296.2, 296.3, 300.4, 309.0, 309.1, 311	Health care + out of pocket payments	6	Adherence	Cost-consequences	Wyeth-Ayerst Research
>=18Y/O								
Polsky et al. (2002)	Fluoxetine (n=840), sertraline (n=386), paroxetine (n=545)	USA	ICD-9-CM 296.2, 296.3	Health care	12	Treatment persistence	Cost-consequences	SmithKline Beecham
18-64 Y/O								
Crown et al. (2001)	Fluoxetine (n=882), paroxetine (n=352), sertraline (n=796)	USA	ICD-9-CM 296.2, 296.3, 300.4, 309.0, 309.1, 311	Health care	24	Guideline adherence	Cost-consequences	Eli Lilly and Company
>=18 Y/O								
Baker et al. (2001)	SSRIs (n=2877), TCAs (n=2303), atypical/heterocyclic agents (n=447)	USA	ICD-9: 296.2, 296.3, 300.4, 311	Health care+ out of pocket payments	12	Guideline adherence (treatment persistence)	Cost-consequences	Pfizer Inc.
No age								

limitations								
Poret et al. (2001) >=18 Y/O	Bupropion SR (n=115), fluoxetine (n=564), paroxetine (n=393), sertraline (n=481), venlafaxine (n=73), TCAs (n=145)	USA	ICD-9-CM 296.2, 296.3, 300.4, 309.0, 309.1, 311	Health care	6		Cost-analysis	None declared
Sullivan et al. (2000) >=19 Y/O	Venlafaxine (n=208), SSRIs (n=332), TCAs (n=191), other ADs (n=250)	USA	ICD-9-CM 296.20-26, 296.30-36, 296.50-296.56, 300.4, 300.9, 296.90, 311.0	Health care	12		Cost-analysis	Wyeth-Ayerst Laboratories
Croghan et al. (2000) 18-64Y/O	Fluoxetine (n=1351), sertraline (n=508), TCAs (n=698)	USA	ICD-9-CM 296.2, 296.3, 300.4, 309.1, 311	Health care	12	Hospitalization	Cost-consequences	Eli Lilly and Company
Berndt et al. (2000) 18-65Y/O	Fluoxetine (n=945), paroxetine (n=492), sertraline (n=905)	USA	ICD-9 296.2, 296.3, 300.4, 311.0	Health care + out of pocket payments	12	Hospitalization	Cost-consequences	Pfizer Inc.
Dobrez et al. (2000) 18-64 Y/O	SSRIs (n=1982), TCAs (n=696)	USA	ICD-9-CM 296.2, 296.3, 300.4, 309.0, 309.1, 311	Health care	12	Treatment persistence	Cost-consequences	Eli Lilly and Company

Griffiths et al. (1999) >=19 Y/O	Venlafaxine (n=188), TCAs (n=172)	USA	ICD-9-CM 296.20-26, 296.30-36, 296.50-296.56, 300.4, 309.0, 296.90, 311.0	Health care	12		Cost-analysis	Wyeth-Ayerst Laboratories
McCombs et al. (1999) 18-100Y/O	TCAs (n=970), heterocyclics (n=311), paroxetine (n=97), sertraline (n=130), fluoxetine (n=140)	USA	ICD-9 296.2, 296.3	Health care	12	Guideline adherence	Cost-consequences	Eli Lilly and Company
Sclar et al. (1999) 18-65 Y/O	TCA(amitriptyline, n=237), citalopram (n=71), fluoxetine (n=411), paroxetine (n=334), sertraline (n=286)	USA	ICD-9-CM 296.2:	Health care + out of pocket payments	6	Treatment persistence	Cost-consequences	Forest Laboratories, Inc. and Parke-Davis division of Warner-Lambert Company
Russell et al. (1999) 18-65Y/O	Sertraline (n=905), paroxetine (n=492), fluoxetine (n=945)	USA	ICD-9 296.2, 296.3, 300.4, 311.0	Health care	12	Treatment persistence	Cost-consequences	Pfizer Inc.

* Only a subsample with depression is reported here

** The average length of the post-baseline period for each individual
ADs: antidepressants

Table 2.2. Characteristics of included papers of prospective studies

Conventional RCTs

Study	Interventions	Country	Cost perspective	Duration of costs/ outcomes	Primary outcome	Economic evaluation	Main results	Sponsor
Wade et al. (2008) 18-65Y/O	Escitalopram (n=141), duloxetine (n=146)	Multisite	Society (healthcare+ loss of productivity)	24 weeks	Change in Sheehan Disability Scale (SDS) score	Cost-effectiveness	Escitalopram was more effective on the SDS score and less costly compared to duloxetine.	H. Lundbeck A/S
Domino et al. (2008) 12-18Y/O	Fluoxetine (n=94), CBT (n=89), fluoxetine+CBT (n=92), placebo (n=94)	USA	Society (healthcare+ family costs)	12 weeks	Change in Children's Depression Rating Scale-Revised	Cost-effectiveness	Fluoxetine was more cost-effective than placebo treatment if the threshold of $100,000 per QALY was applied	Government
Fantino et al. (2007) 18-65Y/O	Escitalopram (n=138), citalopram (n=142)	France	Society (healthcare + loss of productivity)	8 weeks	Remission, Montgomery-Asberg Depression	Cost-effectiveness	Escitalopram probably had better effectiveness (both remission and	H. Lundbeck A/S

			, health care		Rating Scales Self-reported (MADRS-S)		MADRS-S) and a lower cost than citalopram.	
Fernandez et al. (2005) 18-85Y/O	Escitalopram (n=126), venlafaxine (n=125)	Multisite	Health care (with society perspective considered in a sensitivity analysis)	8 weeks	EQ5D	Cost-effectiveness	Healthcare costs were lower for escitalopram compared with venlafaxine. No between-group difference in EQ5D was noted.	H. Lundbeck A/S
Romeo et al. (2004) No age limitations	Mirtazapine (n=93), paroxetine (n=84)	UK	Society (healthcare + loss of productivity) , health care	24 weeks	17-HAMD	Cost-effectiveness	Mirtazapine was probably a cost-effective treatment choice compared to paroxetine according to CEAC.	Organon Laboratories
Patel et al. (2003) >=17 Y/O	Fluoxetine (n=150), placebo (n=150), psychological	India	Health care + patient/ family costs	12 months	Psychiatric morbidity (Revised Clinical	Cost-effectiveness	Fluoxetine was more cost-effective than placebo in the short term and long	Charitable foundation

	treatment (n=150)				Interview Schedule: CISR total score)		term.	

Pragmatic RCTs

Study	Interventions	Country	Cost perspective	Duration	Primary outcome	Economic evaluation	Main results	Sponsor
Serrano-Blanco et al. (2009) 18-65Y/O	Fluoxetine (n=53), imipramine (n=50)	Spain	Society (healthcare + loss of productivity)	6 months	EuroQoL-5D	Cost-utility	Imipramine dominated fluoxetine with 81.5% of the bootstrap replications in the dominance quadrant.	Government
Serrano-Blanco et al. (2006) 18-65Y/O	Fluoxetine (n=53), imipramine (n=50)	Spain	Society (healthcare + loss of productivity)	6 months	Montgomery-Asberg Depression Rating Scales (MADRS)	Cost-effectiveness	The imipramine group had fewer treatment costs than fluoxetine when effectiveness was similar	Government

							between groups.	
Peveler et al. (2005) >=18 Y/O	TCAs (n=111), SSRIs (n=109), Lofepramine (n=104)	UK	Health care	12 months	Depression-free weeks	Cost-effectiveness	CEAC suggested that SSRIs were likely to be the most cost-effective option although the probability of this did not rise above 0.6.	Government
Hosak et al. (2000) No age limitations	Amitriptyline (n=31), citalopram (n=29), fluoxetine (n=30)	Czech Republic	Health care	6 months	Hospitalization-free days	Cost-effectiveness	Neither cost nor effectiveness were significantly different among the treatment groups.	None declared
Simon et al. (1999) No age limitations	Desipramine (n=135), fluoxetine (n=128), imipramine	USA	Health care	24 months	Remission, HDRS, SCL, SF-36	Cost-consequences	The fluoxetine group did not differ from TCA groups on any measure of	Lilly Research Laboratories

	(n=130)						depression severity or quality of life; total medical costs were essentially identical between groups.	

Naturalistic observational study

Study	Interventions	Country	Cost perspective	Duration	Primary outcome	Economic evaluation	Main results	Sponsor
Serrano-Blanco et al. (2006) 18-75Y/O	Fluoxetine (n=100), paroxetine (n=110), citalopram(n=38), sertraline(n=53)	Spain	Society (healthcare + loss of productivity)	6 months	EQ5D	Cost-utility	Fluoxetine dominated paroxetine and citalopram with 63.4% and 79.3% of the bootstrap replications in the dominance quadrant, respectively; fluoxetine was	Government

		cost-effective over sertraline with 83.4% of the bootstrap replications below the threshold of 33,936 US$/QALY.

Findings from economic evaluations comparing antidepressants using prospective study designs

Conventional RCTs

Findings from conventional RCTs were also reviewed. Four of the six conventional RCTs included were head-to-head cost-effectiveness comparisons between antidepressant treatments for patients with major depressive disorder. Three of these compared the cost-effectiveness of escitalopram with duloxetine (for those aged 18-65) (Wade et al., 2008), citalopram (18-65) (Fantino et al., 2007), and venlafaxine (18-85) (Fernandez et al., 2005), respectively. The results revealed that escitalopram appeared as a dominant strategy compared to either duloxetine or citalopram and it had similar effectiveness but lower costs compared with venlafaxine. The other head-to-head comparison examined the cost-effectiveness of mirtazapine versus paroxetine and suggested that mirtazapine may be a more cost-effective treatment choice (Romeo et al., 2004).

In the remaining conventional RCTs, fluoxetine was compared to placebo or psychological treatment for the management of common mental disorders in adults (Patel et al., 2003) and major depressive disorder in adolescents (Domino et al., 2008). Fluoxetine was shown to be more cost-effective than placebo and psychological treatment over both the short term (two months) and long term (12 months) in the former study (Patel et al., 2003) and in the latter one, fluoxetine was more cost-effective than placebo treatment when the threshold of $100,000 per quality-adjusted life year (QALY) was applied (Domino et al., 2008).

With the exception of one study which adopted a healthcare payer perspective with a societal perspective considered in a sensitivity analysis (Fernandez et al., 2005), all the conventional RCTs estimated costs from a broader societal perspective, either healthcare with loss of productivity costs (Fantino et al., 2007; Romeo et al., 2004; Wade et al., 2008) or healthcare with patient and/or family costs (Patel et al., 2003). The outcome measures used in these conventional RCTs included the Sheehan Disability Scale score (SDS), Children's Depression Rating Scale-Revised, Montgomery-Asberg Depression Rating Scales Self-reported (MADRS-S), EQ-5D (a health-related quality of life measure), 17-item Hamilton Depression Rating Scale (HDRS-17), remission, and psychiatric morbidity rated by the Clinical Interview Schedule, Revised (CISR total score). Study periods ranged from eight to 24 weeks, with the exception of Patel et al (Patel et al., 2003) which measured and compared cost-effectiveness over 12 months (Table 2.2).

Pragmatic RCTs and naturalistic observational studies

Compared to conventional RCTs, pragmatic RCTs aim to inform decisions about clinical practice by testing effectiveness with relatively unselected participants and under flexible conditions. There were five pragmatic RCTs and one naturalistic observational study included in this review (Table 2.2). From a societal perspective, imipramine (a TCA) was shown to be a more cost-effective treatment than fluoxetine in a six-month randomised prospective naturalistic study as the similar level of effectiveness was counteracted by lower total costs for the imipramine group (Serrano-Blanco et al., 2006a). Imipramine was also found to dominate fluoxetine (i.e. better outcomes and lower costs) in a cost-utility analysis (Serrano-Blanco et al.,

2009).

The remaining three pragmatic RCTs adopted a healthcare payer perspective. One of them compared TCAs, SSRIs and the modified TCA lofepramine as first choice of treatment for depressive disorder in primary care, and revealed no significant differences between the antidepressants in either outcomes or costs during the 12 months of follow up. The cost-effectiveness acceptability curves suggested that SSRIs were likely to be the most cost-effective option although the probability of this did not rise above 0.6 (Peveler et al., 2005). In a sample of depressed patients in primary care, randomisation to fluoxetine or a TCA (desipramine or imipramine) led to similar clinical outcomes and overall treatment costs for 24 months (Simon et al., 1999). Using the number of hospitalisation-free days as the effectiveness measure, one pragmatic RCT compared groups defined by initial use of antidepressants (amitriptyline, citalopram, and fluoxetine) and revealed no differences in either depression treatment costs or effectiveness over the period of six months (Hosák L et al., 2000).

From a societal perspective, the only non-randomised prospective six-month follow-up naturalistic study showed that fluoxetine dominated paroxetine and citalopram and had a high probability of being more cost-effective than sertraline (Serrano-Blanco et al., 2006b). Overall, half of the included pragmatic RCTs and the naturalistic observational study adopted the healthcare payer perspective while the others estimated costs from a broader societal perspective. The outcome measures in these studies included the EQ-5D, MADRS, depression-free weeks, hospitalisation-free days, HDRS score, the Medical Outcomes Study SF-36 Health

Survey (SF-36), the anxiety and depression subscales of the Hopkins Symptom Checklist (SCL), and remission. The study periods ranged from six to 24 months (Table 2.2).

2.4. Discussion

Summary of main results comparing database analyses and prospective studies

Based on the available evidence from both database analyses and conventional RCTs, depressed patients prescribed escitalopram had lower total healthcare costs than those prescribed other SSRIs, and escitalopram appeared more effective in terms of treatment persistence and clinical symptom measures like Montgomery-Asberg Depression Rating Scales Self-reported (MADRS-S). Compared to venlafaxine, patients prescribed escitalopram in some studies had lower total healthcare costs. The validity of applying these results to depressed patients with anxiety disorder has not been established.

In database analyses, patients using TCAs generally had comparable healthcare costs to those using SSRIs, while in some studies, higher non-depression related costs and lower depression related costs were found for TCA users. Other database studies reported that SSRI users had greater treatment persistence and lower total healthcare costs than TCA users. Different results emerged from prospective studies. From a healthcare payer perspective, patients prescribed TCAs were shown to have comparable costs and clinical outcomes to SSRI users in pragmatic RCTs (Hosák L et al., 2000; Peveler et al., 2005; Simon et al., 1999). However, from a societal

perspective, TCA users in pragmatic RCTs, had similar or even better outcomes but lower total costs than SSRI users (Serrano-Blanco et al., 2006a; Serrano-Blanco et al., 2009).

Without randomisation, the above results comparing TCAs with SSRIs in database analyses may reflect physician choice based on heterogeneous presentations of depressed patients that could not be captured by demographic factors or proxy variables for disease severity used in the included studies. The findings that TCA users had higher non-depression-related costs and lower depression-related costs than SSRI users also implied that in real-world settings, patients prescribed TCAs are probably different from SSRI users in terms of clinical features of depression or comorbid physical illnesses. When randomisation was applied in a pragmatic RCT, TCA users were shown to have equal or better outcomes than SSRI users and total costs were found to be equal or even lower for patients prescribed TCAs. It is also worth noting that the cost-effectiveness advantage of TCAs over SSRIs revealed in the pragmatic RCTs (but not in the database analyses) may not be driven by the lower drug acquisition costs of TCAs considering that the wider societal cost perspective in the pragmatic RCTs would mean the contribution of drug acquisition costs to total costs is very low. Therefore, the cost-effectiveness differentials between TCAs and SSRIs among these studies are likely to be driven by other factors that warrant further research.

Strengths and limitations of economic evaluations using database analyses

Database analyses can supplement RCTs to inform decision-making in actual clinical

practice, as conventional RCTs may not accurately reflect the real-world cost-effectiveness of competing antidepressant treatments (Crown, 2000). Appropriate allocation of scarce resources among competing choices is a fundamental policy concern. Economic evaluations conducted within the context of conventional RCTs may not be sufficient to inform decision-making, considering that individual behaviour in conventional RCTs is controlled through a strict, protocol-driven environment. In light of these considerations, more flexible study designs are employed in pragmatic RCTs to measure cost-effectiveness in a situation closer to the real-world settings. Despite that, the randomisation procedure makes physician choice and other important factors influencing initial choice of antidepressant treatment in real-world settings unobservable.

Economic evaluations based on RCTs may be underpowered. The sample size of an RCT is usually calculated according to clinical rather than economic criteria, and a much larger sample may be needed to determine the significance of economic outcomes (Briggs, 2000). Although modeling and other methods have been widely used in recent economic evaluations, these approaches rely heavily on assumptions that may not be easily testable. By contrast, retrospective database analyses using routine administrative data can offer quick access to large samples of patients in naturalistic settings. Besides the advantages of lower research costs and larger sample sizes than RCTs, database analyses potentially assess economic outcomes over longer periods of follow-up and from more heterogeneous populations, and hence are capable of supplementing RCTs to inform decision-making.

Despite these strengths, several limitations should be borne in mind when interpreting

results from database analyses. Lack of clinical data on effectiveness is clearly a major issue. Many database analyses in this review focus on comparisons of costs. Among studies comparing costs and outcomes simultaneously, persistence of treatment and rate of hospitalisation are frequently used as proxies for clinical effectiveness. There are concerns regarding the use of these proxies; for example, poor outcome tends to be assumed for individuals who discontinue their index antidepressants without taking into consideration fast responders or patients with milder disease severity. The use of hospitalisation rate as an effectiveness index may be problematic as it is also a resource measure (and hence potentially included in the measurement of cost). Also, use of hospitalisation is influenced by its supply. Efforts to develop alternative methods for obtaining effectiveness measurements have been noted in the literature, such as the application of expert panels to estimate health values (as an effectiveness index) of alternative treatment patterns (Watkins et al., 2009). In that study, a panel of 13 clinical experts made a series of utility ratings for a range of clinical profiles before any new treatment, three months later with no new treatment and three months after initiating various common treatments. Clearly, further efforts should be made to incorporate newer approaches to effectiveness measurement in administrative database analyses.

Compared to the more recent RCTs, database analyses usually adopt a narrower definition of costs, do not include services outside the health area, and so are unlikely to adequately detect the impact of treatment on loss of productivity and employment and other areas that may contribute substantially to the overall costs of depression (Thomas and Morris, 2003; Wang et al., 2003).

There are also biases to be considered in database analyses. Confounding or selection bias due to nonrandomised study design is clearly important. For example, a patient's medical and social history, disease severity, and a physician's characteristics may influence both the initial choice of antidepressant and the subsequent outcome. To address this heterogeneity issue, strategies including matching (Sheehan et al., 2004) and the use of propensity score techniques (Wade et al., 2010) have been used. Furthermore, the reverse causality between medical care utilisation and drug choice can be minimised through defining the drug choice at baseline and estimating utilisation during the following period. While this limits potential attempts to compare treatment effects in a counterfactual scenario using database analyses, it also is cognizant of the real-world situations in which physician preferences and heterogeneity of clinical presentations influence both antidepressant choice and cost-effectiveness outcomes for a patient with depression.

Publication/sponsorship bias would be another major concern as complex statistical analyses could leave the results open to a degree of subjectivity. Since 23 out of the 28 database analyses included in this review were sponsored by the pharmaceutical industry and another three studies had authors affiliated with pharmaceutical companies, the potential for overestimation of effect due to sponsorship should be kept in mind, especially when no company has apparently published data that indicate their compound to be less cost-effective than a rival. Of course, this consideration applies to many randomised trials too.

In this review, the antidepressant of interest was usually new or just available in the months leading up to the study, while the comparator drugs were mostly well

established and continuously available. Many physicians might not be able to prescribe newer antidepressants in the beginning of the study period and might have had inadequate time to gain sufficient experience with them. Some of them might preferentially prescribe newer antidepressants to those patients refractory to previous treatment, a tendency that has been called ‘channeling’ or ‘allocation bias’ (Egberts AC et al., 1997). However, the reverse might also be true, if not more common, i.e. to prescribe newer antidepressants to patients with milder disease to gain more clinical experience while the perceived mild side effects would not harm patients. For example, patients who are able to work may be prescribed newer agents because these drugs are perceived as less disruptive and more tolerable. The timing of studies therefore might affect the economic outcomes presented due to the different intervals from the launch dates of competing antidepressants.

Furthermore, diagnostic heterogeneity in the studied populations was noted (Table 2.1). These differences may act as confounders when assessing the relative cost-effectiveness of the various antidepressants.

Although most of the included database analyses adopted an intention-to-treat (ITT) design, this approach may not be directly transferrable from the analysis of RCTs where it was originally used. The most important aim of ITT is to maintain treatment groups that are similar apart from random variation. In database analyses, patients are of course not randomised to treatments and the possibility for selection bias must be addressed by statistical methods other than ITT analysis. Furthermore, the second fundamental idea behind ITT is to reduce bias that might be introduced by excluding patients who did not complete the originally assigned course of therapy from the

analyses (Gillings D and Koch G, 1991). Yet, most database analyses excluded those not continuously enrolled in the insurance programme during the study period, hence bringing in possible bias.

With the exception of one study from the United Kingdom (Wade et al., 2010), all the database analyses are from the United States or Canada and so all studies are from Western developed countries. Generalisability of effectiveness and cost data across different countries might not be straightforward. Not only do prescribing costs differ dramatically between settings, but also healthcare systems are organised in very different ways. Differences are certainly evident when comparing high- to low- and middle-income countries (Dixon et al., 2006; Knapp et al., 2006). Moreover, many of the included studies are based on private insurance databases in which the subjects might be healthier, with different socioeconomic characteristics, or provided with different antidepressant choices compared to people with public insurance or no insurance (Chung, 2005; McCombs et al., 1999). Future research is needed from developing countries and covering different insurance systems, as well as a wider range of populations.

Cost-effectiveness data for populations with different characteristics/comorbidity are not available. Despite studies comparing the characteristics across subjects initially treated with individual antidepressants, there have been no cost-effectiveness comparisons of individual antidepressant treatments across specific populations with different needs.

2.5. Implications

This review suggests database analyses are an important source of evidence of the potential cost-effectiveness of alternative antidepressant treatments. Even though database analyses are susceptible to bias and confounding, they have the advantage of being based on observations from real-world practice. Given the limited external validity of RCTs, database analyses using data from actual clinical practice can usefully contribute to our understanding of the economic outcomes of alternative antidepressant treatments. Prospective and retrospective studies have their own strengths and limitations. It is essential to assess economic outcomes across a broad range of contexts using a range of study designs, and only findings that are consistent across a number of study designs and healthcare settings should be accepted with confidence.

Specific implications for the methods of database analyses for this thesis

To date, few economic evaluations based on database studies have evaluated costs and outcomes simultaneously and the outcome measures used in previous studies are not able to directly represent targets of clinical treatment, like remission. Future economic evaluations should aim to identify more suitable outcome measures which could reflect clinical practice and to evaluate costs and outcomes simultaneously using appropriate methods of economic evaluation.

This review has found that head to head comparisons between individual antidepressants more commonly use RCTs while comparisons between whole

categories (e.g. SSRIs vs. TCAs) are more prevalent in database analyses. However, few studies have compared more than two categories of antidepressants at the same time while physicians need to choose between various antidepressants given the range of categories. Therefore, economic evaluations comparing multiple categories of antidepressants in the depression treatment are needed. Furthermore, in order to make comparisons across disease areas, generic outcome measures should be incorporated into future economic evaluations if comparisons are to be made with interventions in other clinical areas.

Chapter 3. Study design and economic evaluation methods

The purpose of this chapter is to consider the suitability of different study designs, and methods used in economic evaluations for comparing antidepressant treatments. Given the focus on database analyses in this thesis, strengths and limitations of different study designs and economic evaluations for the proposed analyses in this specific study context are also discussed.

3.1. Study design

Observational studies

Given the focus in this study on the 'real-world' cost-effectiveness of antidepressant treatments, an observational study design was chosen. There are several observational designs which can be defined as follows (Centre of Reviews and Dissemination, 2001).

- Cohort study: A comparison of costs and outcomes is made between participants who have received an intervention and those who have not.
- Case-control study: Participants with and without a given outcome are identified and exposure to a given intervention is compared. Costs are compared by exposure and outcome status.
- Cross-sectional study: The relationships between a disease, costs, and other variables of interest (e.g. demographic and clinical) are examined in a defined population at a particular time.
- Before-after study: The comparison is made between costs and outcomes before

and after an intervention is implemented.

- Case series study: A description of cost and outcomes of a number of cases who received an intervention.

Black (1996) identified circumstances in which non-randomised approaches may be appropriate, or even preferred, to randomised studies because of the nature of a study (Black, 1996). First, experimentation is unnecessary if the effect of the intervention is believed to be so strong that the likelihood of unknown confounding factors affecting the results is too small to warrant attention. Second, experimentation may be inappropriate in cases where it would be impossible to recruit sufficient numbers to measure a rare outcome including one that takes place in the future, or to determine the impact of uncommon adverse events. Neither is considered to be a concern here as outcome of depressive illness is likely to be influenced by multiple factors and the ailment and its treatments both can have a short-term effect as well as longer-term consequences.

Third, randomised controlled trials (RCTs) may be inappropriate where randomisation itself impacts upon the effectiveness of the intervention. It is suggested that this would be the case where the intervention requires the subject's active participation, which would depend on their beliefs and preferences (Black, 1996). This will certainly be a concern here because individual patient's active participation is important for antidepressant treatments. The attrition rate of antidepressant treatments is high in both trials and naturalistic settings. The adherence is usually poorer in ‘real-world’ situations than in trials. For example, attrition rates in the first three months of treatment can be as high as 52% in naturalistic settings (Lin et al., 1995; Maddox et

al., 1994). Such poor adherence to antidepressants may reduce the effectiveness of treatment (Demyttenaere et al., 2008). As patients' beliefs about the cause of depression and preferences towards antidepressants can influence both adherence and outcome, randomisation precludes patients' participation in decision-making which may impact the effectiveness of the intervention. Additionally, experimentation may be impossible when key personnel involved in the delivery of the intervention are unwilling to participate in an RCT. Physicians may tend to prescribe to patients different antidepressants other than the allocated ones when this is allowed. In a previous cost-utility study, a higher proportion of patients randomised to TCAs were in fact prescribed a different class of antidepressants than those randomised to SSRIs (TCA: 42% vs. SSRI: 16%) and physician preference was the stated cause for over half of these cases who did not receive the allocated treatment (Kendrick et al., 2006). Therefore, it is not always appropriate to assume that physicians would prescribe antidepressants randomly to their patients.

Experimentation may also be inadequate if there is only limited scope for the results to be generalisable to other settings. Black (1996) notes that the more complex the intervention, the lower the external validity. For example, the results noted in trials undertaken with well-trained enthusiastic professionals in teaching hospitals may not be replicable elsewhere. Since depression is a highly prevalent disease and usually treated in routine practice settings, it is not likely that the treatment and resources provided in trials could be replicated in everyday practice.

Finally, strict inclusion and exclusion criteria in RCTs often mean that trials include only a small proportion of the patients that are treated in usual practice. Although

these limitations of RCTs can be overcome to some extent through modifying study protocols, e.g. pragmatic RCTs, with randomisation maintained, an economic evaluation based on an observational study design for a total-population sample can be helpful to supplement results from clinical trials and to answer real-world cost-effectiveness questions that are of interest to policy makers. However, it should be kept in mind when interpreting results from observational studies that lack of randomised comparisons can be a limitation.

It is useful to make a distinction between efficacy and effectiveness trials (Table 3.1). Efficacy trials take place under strict conditions regarding the treatments received by the intervention and control groups and seek to prove that the intervention works, i.e. to prove the effect of the treatment relative to the a control in the ideal situation where all persons fully comply with the treatment regime (Everitt, 1995). Effectiveness studies, sometimes called pragmatic trials, are observational and seek to demonstrate whether an intervention works in real-world settings (Hotopf, 2002).

Table 3.1. Differences between efficacy and effectiveness trials

	Efficacy trials	*Effectiveness trials*
Aim	To establish the efficacy and safety of a specific clinical intervention	To establish the effectiveness of approved treatments, interventions, programmes or policies
Timing	Prior to the intervention being introduced	Post-implementation
Diagnosis	Structured interview	Clinical diagnosis or structured interview
Inclusion/exclusion criteria	Strict, tending to exclude patients with co-morbid disorders	Limited, in order to maximise external validity
Comparator	Placebo, active control or treatment as usual	Active comparator or treatment as usual
Blinding	Patients, staff and researchers blind to treatment allocation	Blinding whenever possible
Research protocol	Strictly defined	Designed to be closely aligned to treatment as usual
Outcomes	Clinical parameters such as symptom rating scales	Single primary outcome measure with multiple secondary outcomes including costs

Adapted from Tansella et al. (2006)

Observational studies, designed to be closely aligned to routinely delivered care, can have better external validity and generalisability. However, despite the fact that observational studies may provide information regarding whether an intervention works in real-world settings, caution should be borne in mind when interpreting

results because allocation to the treatment groups is not generally randomised and any results may be subject to confounding. Thus it is very challenging to differentiate between groups in terms of outcomes due to unobserved factors (Everitt, 1995) and oftentimes, more complex statistical methods are needed in analysing results from observational studies.

3.2. National Health Insurance Research Database (NHIRD)

This study uses data from the National Health Insurance Research Database (NHIRD) in Taiwan. National Health Insurance (NHI) in Taiwan is a single-payer compulsory social insurance plan that centralises the disbursement of healthcare funds and guarantees equal access to health care for all citizens. With a coverage rate of over 98% (Wu et al., 2012), nearly all Taiwanese citizens sought care through NHI (Chan et al., 2006). The enrolled person is issued an NHI card, which serves as an identification card to access the medical system. The NHIRD provides information of insured residents' health care utilisation (medical contacts and procedures/treatments), expenditure, demographic characteristics of users, and practicing features of physicians (e.g. physician specialties and types of hospitals in which the physicians work). Clinical diagnoses are coded in the NHIRD according to the International Classification of Diseases, 9th revision, clinical modification (ICD-9-CM).

The main registration and claims datasets maintained in the NHIRD are as follows (Hsiao et al., 2007):

(i) Registry for beneficiaries: Registry for beneficiaries allows follow-up and identification of insured persons. Data elements include date of birth, gender, and

unit/type of enrolment. A unique identification code is assigned to each person insured and precautions are taken to safeguard the confidentiality of individually identifiable information.

(ii) Registry for contracted medical facilities and medical personnel: This includes two separate files containing data on the NHI's practicing healthcare facilities and professionals. The type and location of the facilities and the demographic information of the healthcare professionals are specified.

(iii) Outpatient visits: There are two subsets of databases providing information on outpatient visits, which are the 'ambulatory care expenditures by visits' and the 'details of ambulatory care orders'. The outpatient visit database is an encounter form-based dataset with date of each visit, diagnosis codes, type of providers, health professionals, and service costs.

(iv) Inpatient visits: Two subsets of databases provide information on inpatient visits, which are the 'inpatient expenditures by admission' and the 'details of inpatient care orders'. The inpatient visit database is also an encounter form-based data set with date of each admission, diagnosis codes, procedure codes, type of providers, health professionals, and service costs.

(v) Pharmacy database: This includes all relevant information of prescription drugs dispensed by contracted pharmacies in NHI in Taiwan. Pharmacy identifier, prescribing date, dosage, prescription duration in days, prescribing physician, dispensing pharmacist and cost of prescription drugs are all included.

To ensure the accuracy of disease diagnosis in the NHIRD, the Bureau of National Health Insurance (BNHI) in Taiwan has randomly reviewed medical charts of 1/100 ambulatory and 1/20 inpatient claims on a regular basis (Wang et al., 2013).

Furthermore, the high validity of the diagnostic data from the NHIRD has been reported (Cheng et al., 2011), although future studies to further validate diagnoses of specific mental disorders may still be needed. Regarding the quality of service use data, agreement between self-reported utilisation and the insurance claims of the NHIRD was shown to be good in the general population in Taiwan (Yu et al., 2009). Data from the NHIRD can be considered as representative of the total population sample that encompasses the entire range of clinical diversity of depression and the contexts of clinical contacts, e.g. outpatient or inpatient settings. During the past decade, there have been a large number of published studies based on the NHIRD in Taiwan (see Chapter 1).

Study cohort details

The cohort is defined as all subjects in the NHIRD receiving at least one antidepressant prescription for treatment of major depressive disorders (MDD; ICD-9-CM codes: 296.2x, 296.3x) or other depressive disorders (ICD-9-CM codes: 311.xx, 300.4x) in 2003. The index date is defined as the date in 2003 on which the subject is first identified in NHIRD. A dataset containing all NHI information of the subject in the preceding one year and the three years following the index date was then established. Only data on adult subjects (aged 18 or over on the index date) are included in the analyses of this thesis.

Demographic and clinical data

Demographic and clinical data, including age, gender, physician specialty, clinical

setting (inpatient, outpatient and emergency departments), types of depression (MDD, other depression) and choice of antidepressants on the index date were extracted. Subjects were further divided into groups of newly diagnosed and pre-existing depression (non-newly diagnosed depression). Subjects with newly diagnosed depression were defined as people who had not received antidepressant treatment or a depression diagnosis in the twelve months prior to the index date. Limitations of the definition of newly diagnosed depression include mis-categorising patients who had been treated for depression at an earlier time, e.g. two years ago.

Categories of antidepressants included selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), other older antidepressants (maprotiline, moclobemide, and trazodone), other newer agents (bupropion and mirtazapine) and multiple use of antidepressants at the index date (including more than one from the same class).

Comorbidity data

Data on comorbid mental disorders, physical disorders and painful physical symptoms during the twelve months before the index date were extracted. These variables indicated presence or non-presence of the comorbidities. The included comorbid disorders are listed in Tables 3.2, 3.3 and 3.4.

Table 3.2. Comorbid mental disorders extracted from NHIRD

Category	ICD-9-CM
Schizophrenia	295
Other psychotic disorder	297.0-297.3, 297.8-297.9, 298.1-298.4, 298.8-298.9
Transient psychotic disorder	293.81, 293.82
Paranoid personality disorder	301.0
Substance induced mental disorder	303-305
Alcohol induced mental disorder	291
Drug induced mental disorder	292
Bipolar spectrum disorder	296.0-296.1, 296.4, 296.6-296.7, 296.80, 296.81, 296.89
Dementia and related disorder	290, 291.2, 292.82, 294.1, 294.8, 331
Generalised anxiety disorder	300.02
Obsessive-compulsive disorders	300.3
Panic disorder without agoraphobia	300.01
Phobic disorder	300.2
Post-traumatic stress disorder	309.81
Acute reaction to stress	308
Sleeping disorder	307.42, 307.44-307.47, 347, 780.52, 780.54, 780.59
Hyperkinetic syndrome	314

Table 3.3. Comorbid physical disorders extracted from NHIRD

Category	ICD-9-CM
Cardiovascular diseases	306.2, 394-398, 402, 410-417, 420-429, 431, 434, 436, 437, 746
Chronic obstructive pulmonary disease	490-494, 496
Diabetes Mellitus	250
Hyperlipidemia	272
Hypertension	401-405, 416.0, 416.8, 437.2, 459.1, 459.3, 642
Renal disease	250.4, 403, 404, 581.9, 582-588, 593.9, 646.2, 753.11, 753.15
Stroke	431, 434, 436
Cancer	140-208
Epilepsy	333.2、345
Irritable bowel syndrome	564.1
Rheumatoid arthritis	714
Osteoarthrosis	715

Table 3.4. Painful physical symptoms extracted from NHIRD

Category	ICD-9-CM
Joint (OA, RA, Gout/other, other joint disease, TMJ)	274.0-274.9, 524.62, 712-716, 718-719
Back	720-724
Muscle (myositis, sprain, synovitis/ tendinitis)	840-848, 729.1, 905.7
GU/gastritis	531-535、787.1、V127.1
Functional GI disorder	564.1, 564.5, 564.8, 564.9
Abdominal pain	789.0
Headache/migraine or dizziness	307.81, 346, 386, 780.4, 784.0
CAD/angina or chest pain	413, 786.50, 786.51, 786.59
Other pain (trigeminal, causalgia, phantom limb etc.)	307.80, 307.89, 379.91, 388.70, 350.1, 350.2, 353.6, 354.4, 355.0, 355.37, 729.2, 729.5

Service use and cost data

Service use data extracted from the NHIRD included contacts with outpatient services, emergency department attendances, and days in hospital (for all reasons). Medication data included prescriptions for all medications but only antidepressant medications were specifically identified and analysed in this study. All medication costs were included in the analyses. Service use data for the preceding year (baseline period) and three years following the index date were extracted. The percentage of patients with at least one contact and the mean number of service contacts was reported. The database contains actual expenditure data and no unit costs were separately defined. The assumption used here is that expenditure data represents 'costs'. Annual expenditures were calculated from the actual claims data, were categorised as psychiatric and non-psychiatric expenditures (depending on physician specialty of the service contact) and were converted using purchasing power parity (PPP) conversion rates from New Taiwan Dollars (NTD) to international dollars (World Economic Outlook (WEO) data).

3.3. Analysis of cost differences and variations

Differences in total costs over twelve months between antidepressant groups were initially compared using ANOVA followed by multivariable regression models. Cost data are usually skewed because a small number of individuals in the sample may incur high costs (e.g. prolonged inpatient stays). Transformation is a way of addressing this but the focus on the arithmetic mean cost is usually preferred and so transformation may not be advisable (Thompson and Barber, 2000). Skewed data can

also cause problems for multivariable analyses as the assumptions of standard ordinary least-squares (OLS) linear regression (e.g. normally distributed residuals or homoscedasticity) may be violated. These problems are not though so great when sample sizes are large. In studies where randomisation is not used, multivariable analysis is important for assessing the effect of a specific factor in costs due to the need to control for confounding factors. Therefore, multivariable approaches are employed for the cost analysis in this thesis with the results presented in Chapter 4.

Introduced by Nelder and Wedderburn (1972), the generalised linear model (GLM) synthesises the techniques used to analyse continuous and discrete data into a unified framework (Drummond et al., 1997). This model allows a generalisation of the response distribution to other members of the exponential family, including gamma, inverse Gaussian, and binomial distributions. Also, a description of the variance as a function of the mean has been introduced as a method of modelling cost data (Blough et al., 1999; Manning and Mullahy, 2001). The gamma distribution has been found to be often appropriate for cost analyses given the assumption that data have a constant coefficient of variation, which is frequently the case with cost data. The gamma model may incorporate a reciprocal, log or identity link. In a GLM, the regression equation is called the 'linear predictor' but this linear predictor is not equated with the expected cost, as in multiple regression with the raw data, but via 'link function'. For example, there can be models in which the natural logarithm of the expected costs is equated with the linear predictor (Dunn et al., 2003). The log link is also commonly used when analysing cost data, because it guarantees non-negative outcomes and has a close connection to the logarithmic transformation of data (Myers et al., 2001). Evidence has suggested that healthcare resource use and expenditure data frequently

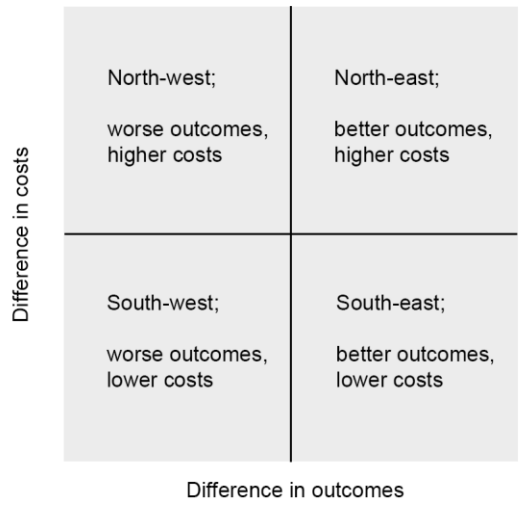
have a log-normal or gamma distribution and the existing studies using GLM for cost analysis have focused on the latter (Manning and Mullahy, 2001). This GLM approach has been commonly used in analyses of economic cost data (Chong et al., 2013; Desai et al., 2013; Sabes-Figuera et al., 2012). Given the characteristic properties of cost data mentioned above, cost analyses in this thesis were conducted by using GLM with a log link and gamma variance function.

3.4. Analysis of cost and outcome

Incremental analysis of costs and outcomes

The most common approach of combining the costs and outcomes in healthcare research is incremental analysis (Drummond et al., 1997; NICE, 2008). In incremental analysis, the additional or incremental costs of the programme are compared to the additional or incremental outcomes. Consider a new intervention for a health problem which is compared to standard treatment, with costs and outcomes measured. Comparing the costs and outcomes will result in one of the four situations, shown in Figure 3.1.

Figure 3.1. Cost-effectiveness plane

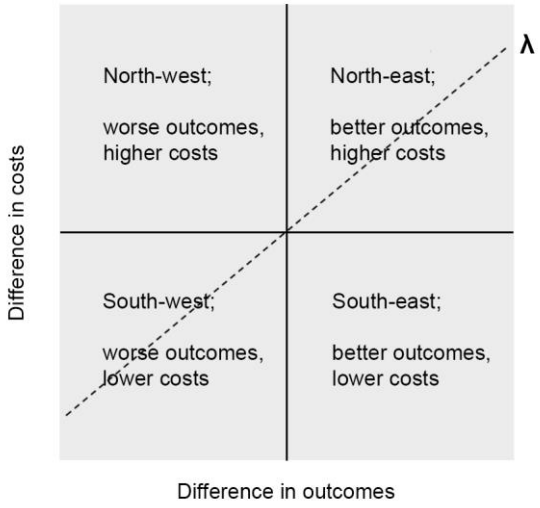


The new intervention could cost less than the standard treatment and result in better outcomes. In this situation the intervention is said to 'dominate' standard treatment and is the preferred choice. The new intervention could cost more than the standard treatment and result in worse outcomes. In this situation, the new intervention is said to be 'dominated' by standard treatment and should not be recommended. The new intervention could cost more than the standard treatment and result in better outcomes. In this situation, there is a trade-off to be made. The decision-maker should be presented with information regarding the incremental cost per incremental unit improvement in outcome in the form of an incremental cost-effectiveness ratio and then the decision maker would need to make a value judgement regarding the intervention. Finally, the new intervention could cost less than the standard treatment and results in worse outcomes. In this situation, there is again a value judgement to be made – are sufficient costs saved to justify the worse outcomes attained?

When non-dominant situations occur (i.e. South West and North East quadrants) then

decision makers need to refer to the incremental cost-effectiveness ratio (ICER) defined as the difference in costs between the two options divided by the difference in outcomes. The ICER can be judged against a maximum *willingness to pay* for improvements in outcome. This willingness to pay for improvements in outcome is often referred to as the ceiling ratio and frequently depicted as λ (Figure 3.2). If the ICER is less than the ceiling ratio (i.e. it falls below the λ line) then the new intervention is considered to represent good value for money. If the ICER is greater than the ceiling ratio (falls above the λ line) then the new intervention is not considered to be cost-effective.

Figure 3.2. Cost-effectiveness plane (with λ indicating hypothetical ceiling ratio)



However, there are problems with the ICER as a summary statistic. The first is that it is based on four sample means and is calculated whether or not the differences in costs or outcomes are statistically significant (Briggs, 2001). One option is to generate confidence intervals for the ICER, which can be calculated using bootstrapping (Barber and Thompson, 2000) and this will be discussed later in this chapter. The second problem is that a negative ICER can occur for two reasons. If the difference in

mean cost is negative and the difference in mean effects is positive, the new intervention is cost-effective. However, a negative ICER could also be produced when there is a positive difference in mean costs and a negative difference in mean effects. Then, the new intervention falls in the north-west quadrant and is not cost-effective

Cost effectiveness acceptability curves

Another commonly-used method for comparing cost and effectiveness simultaneously is to use cost-effectiveness acceptability curves (CEACs) that will be applied to the cost-utility analysis in Chapter 7. CEACs can be constructed using the net benefit approach (Briggs, 2001; Briggs et al., 1997). The net benefit equation is defined as:

$$NB = \lambda * \triangle E - \triangle C,$$

where λ = threshold value, $\triangle E$ = difference in effects between study arms, and $\triangle C$ = difference in costs between study arms.

A net benefit approach was used in the analyses of this thesis. Net benefits for the sample using values for λ (i.e. willingness to pay for an additional quality-adjusted life-year (QALY)) ranging from NTD 0 - NTD 3,000,000 (approximately £60,000) were calculated. Regression models were constructed to estimate the difference in net benefit between study groups and bootstrapping used to produce 1000 differences for each value of λ. (Bootstrapping is a non-parametric approach to analysis that is based on resampling from sample data with replacement (Efron and Tibsirani, 1993).) The proportion of these replications that were greater than zero indicated the probability

that the treatment of interest was more cost-effective than the alternatives (coded as zero) for that value of λ. Plotting these probabilities on a graph created a CEAC, which depicted graphically the probability that the treatment of interest was most likely to be cost-effective (Fenwick et al., 2001; Fenwick et al., 2004). These curves incorporate both the uncertainty that exist around the estimates of mean costs and effects as a result of sampling variation and the uncertainty regarding the maximum cost-effectiveness ratio that a decision-maker would consider acceptable (Fenwick and Byford, 2005).

CEACs assess the likelihood of the treatments of interest being more cost-effective than the alternative for a range of willingness-to-pay values for an additional unit of outcome (e.g. a QALY). This approach assumes that there is a theoretical but unknown value that society would place on an improvement in outcomes. In this thesis, the threshold was assumed to be between NTD 1,500,000 (£30,000) and NTD 2,000,000 (£40,000) (Shiroiwa et al., 2010).

Sensitivity analyses

Because every evaluation contains some degree of uncertainty, imprecision or methodological controversy, sensitivity analyses were applied in this thesis, i.e. critical methodological assumptions or areas of uncertainty were identified and then different assumptions or estimates employed in order to test the sensitivity of the results and conclusions to such changes. If large variations in the assumptions or estimates underlying the analysis do not produce substantial alterations in the results then one would tend to have more confidence in the original results. If the converse

occurs, more effort is then required to reduce the uncertainty and/or improve the accuracy in estimating the values of the critical variables.

There are a number of sources of uncertainty in economic evaluation. First, no data may be available and expert-informed estimates are required. This may be the case for estimates of the effectiveness of new technologies. Second, estimates may be available but they may be known to be imprecise. For example, only the average cost per day may be known for estimates of hospital costs. Third, there may be methodological controversy about some parameter values. This may be the case for analytic decisions such as the choice of the source of values for health state preferences as in this thesis. Finally, the analyst may use sensitivity analysis to explore the generalisability of study results to other settings. Sensitivity analysis typically involves three steps:

(1) identify the uncertain parameters for which sensitivity analysis is required; (2) specify the plausible range over which uncertain factors are thought to vary; and (3) calculate study results based on combinations of the best estimate and most conservative and least conservative estimates.

All variables in the analysis are potential candidates for sensitivity analysis. Possible reasons for exclusion could be that parameter estimates are known with absolute certainty, or that a preliminary analysis shows that, even if the variable is allowed to vary over a wide range, this has a minimal impact on the overall study results.

3.5. Summary

In this chapter, strengths and limitations of study designs using the proposed database analyses were discussed. For example, it is ‘expenditures’ that were analysed in this thesis under the assumption that these represent ‘costs’. However, ‘expenditures’ may not reflect ‘true costs’ which should be borne in mind while interpreting the related findings. The NHIRD and methods for data extraction were described as well as the proposed approaches of evaluations, e.g. CEACs and sensitivity analysis.

Chapter 4. Costs of care received by patients with depression and analysis of cost variations

The purpose of this chapter is to identify which demographic and clinical characteristics and comorbidities are associated with healthcare costs with a particular focus on comorbid pain and cardiovascular diseases. Cost comparisons between patients using different categories of antidepressants are also examined. Analyses are conducted on different cost categories, i.e. psychiatric, non-psychiatric, and total costs. Generalised linear modeling is employed to control for confounding factors when making comparisons.

4.1. Introduction

The total direct healthcare costs of depression in Taiwan rose by 50% over the period of 2000-2002 (Chan et al., 2006). Furthermore, the prevalence of antidepressant use doubled from 1997 to 2004 (Chien et al., 2007a). These results based on analysis of NHIRD data could imply an increase in the need for depression treatment, a reduction in the treatment gap, or over-provision of care. Future research is needed to determine the true cause of the phenomena.

As mentioned in previous chapters, the National Health Insurance (NHI) in Taiwan is a single-payer compulsory social insurance plan that guarantees equal access to health care for all citizens. Patients can freely choose between providers and have direct access to specialist care without going through a gatekeeper or referral system. There is also no limit to the number of visits a patient can make to services (Chen et al.,

2007). Given the all-inclusive nature of this system and relatively affordable co-payments, it seems reasonable to anticipate a further rise in healthcare costs for patients with depressive disorders. It is thus particularly important to assess the impact of depression treatments on both expenditures and related outcomes in the context of the insurance system in Taiwan.

As seen in Chapter 1, depressive disorders are known to be associated with a variety of physical conditions (Katon, 2003), certain of which warrant further research. Depression and cardiovascular diseases (CVD) are projected to be the first and second leading causes of health-related burden in 2015 (WHO, 2008). Currently, depression is found to be among the top-ranking causes of global disability (Vos et al., 2012), while CVD constitutes the leading cause of premature death (Lozano et al., 2012). These two conditions frequently co-occur (Joynt et al., 2003) and there is accumulating evidence suggesting close interrelationships between them (Sorensenf et al., 2005; Thombs et al., 2006). For example, depressive symptoms have been found to be a risk factor for cardiac events in patients with coronary heart disease (Barth et al., 2004; van Melle et al., 2004). Given that the two conditions co-occur it is useful to evaluate the impact of comorbid CVD when performing economic analyses of treatment for depression.

Another disease entity, painful physical symptoms (PPS), may also be of importance when assessing the economic impact of treatment for depression. Previous studies have revealed a high prevalence of pain complaints in depressed patients (Bair et al., 2004; Bair et al., 2003; Husain et al., 2007; Ohayon and Schatzberg, 2003) and outcomes of treatment for depression may be poorer in the presence of PPS (Fava et

al., 2004; Gameroff and Olfson, 2006; Leuchter et al., 2010). The severity of pain seems to be a strong predictor of poor treatment response to antidepressants as well as impaired quality of life outcomes after initial treatment (Bair et al., 2004) which may lead to a more severe and chronic relapsing course (Judd et al., 2000). Evidence also suggests a relationship between increased healthcare costs and the presence of comorbid moderate to extreme pain interference among patients with major depressive disorder (MDD) (Gameroff and Olfson, 2006). It is thus reasonable to assume that there are impacts of PPS on patients' help-seeking behaviours and treatment costs.

CVD and PPS may also have greater effects than other physical comorbidities on the choice of antidepressants or on treatment outcomes. Individual antidepressants are shown to have a wide range of cardiovascular effects (Taylor, 2008), which would be a great concern for treating depressed patients with comorbid CVD. Conversely, treating PPS in patients with depression has been an emphasis of pharmaceutical research during the past decade. Individual antidepressants may differ in their effectiveness for the relief of PPS (Sullivan and Robinson, 2006) and classes such as serotonin norepinephrine reuptake inhibitors (SNRIs) have been reported as particularly effective in reducing pain. Given the above characteristics, the presence of co-occurring CVD and PPS may influence the choice of antidepressants, with a potential impact on healthcare costs. Besides physical comorbidities and choice of antidepressants, treatment history, as well as comorbidities of mental illnesses, should also be taken into consideration when analysing costs of depression treatment.

This chapter seeks to measure healthcare costs from the healthcare perspective for

people with depression using claims data from the NHIRD in Taiwan. The specific objectives are to identify which demographic and clinical characteristics and comorbidities are associated with total healthcare costs, as well as costs for specific groups of services, with a particular focus on comorbid pain and CVD.

4.2. Methods

Data

Data on all NHI information for each subject of the identified cohort (see inclusion criteria below) were extracted for the two-year period spanning the index date (one year preceding, and one year following). As stated in Chapter 3, the available data included the preceding year before and the following three years after the index date. In this chapter, only analyses of the costs for the following one year are given because it would be difficult to interpret relationships between variables of interest at baseline and costs for the whole three years. The impact of initial *outcomes* on costs for the consecutive three years after the index date will be analysed and discussed later in Chapter 6.

Participants

All subjects in NHIRD meeting the following criteria were included:

- At least one prescription for an antidepressant for treatment of MDD (ICD-9-CM codes: 296.2x, 296.3x) or other depression (ICD-9-CM codes: 311.xx, 300.4x) in 2003.

- Data available for a minimum of 12 months before and after the index date.
- Age 18 years or over on the index date.

As defined previously in Chapter 3, a subsample of patients with newly diagnosed depression was also identified within this overall sample (operationally defined as individuals who were free of antidepressant use or a depression diagnosis for a minimum of 12 months before the index date).

Demographic and clinical information

Demographic and clinical data were extracted, including age, gender, diagnosis of depressive disorders, and initial choice of antidepressants on the index date. Participants were further grouped according to past treatment history, i.e. newly diagnosed depression and non-newly diagnosed depression.

Baseline characteristics were traced back for all included subjects for the 12 months prior to the index date, including comorbid mental disorders, physical illnesses (CVD, diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), renal diseases, and cancer), PPS (backache, headache, musculoskeletal and gastrointestinal pain), and healthcare utilisation/expenditure. Because many physical comorbidities co-occur (CVD and DM), inclusion of all these physical comorbidities (other than CVD and PPS) into the model helps to estimate potential confounding effects from other comorbidities.

Service use and costs

Service use data extracted from the NHIRD included outpatient visits, emergency department attendances, and inpatient stays. Service use over the 12-month study period was described by the percentage of patients with at least one unit of service use and the mean number of service contacts. Medication use regarding prescriptions of antidepressants was identified. Annual costs (including all medication costs) were calculated from the actual claims data, were converted by purchasing power parity (PPP) conversion rates and expressed in international dollars (World Economic Outlook (WEO) data).

Data analysis

Sociodemographic data, clinical characteristics, baseline healthcare utilisation/expenditure, and initial antidepressant treatment were described for the overall sample and compared between newly diagnosed depression and non-newly diagnosed depression groups. To identify characteristics predictive of healthcare costs over the 12-month period, univariate analyses were first performed. Then a multivariable generalised linear regression model with a log link and gamma variance function was employed (McCullagh and Nelder, 1989). Separate models were run for total healthcare costs, psychiatric costs, and non-psychiatric costs. To measure the model fit, the root mean square error (RMSE) (Zheng and Agresti, 2000) for each model was computed after excluding 0.1% of subjects with extremely large predicted values in costs. The independent variables considered were age, sex, index depression diagnosis, past treatment history, initial choice of antidepressants, baseline comorbid

mental/physical disorders, baseline PPS, and baseline total healthcare expenditure. These variables were first selected based on the univariate analyses and those significant at the 5% level were subsequently included. A backward selection process was then applied to obtain the final multivariable model, again using a 5% level of significance. Such analyses were subsequently performed in a subsample of subjects with newly diagnosed depression to determine whether having a past treatment history influenced costs.

As use of psychiatric emergency and/or inpatient services may be indicators for patients who require more intensive care, thus generating higher costs, variations in use of these two key services were further examined. Use of these services was represented by binary variables in a multivariable logistic regression model and independent variables were entered using a forward LR (likelihood ratio) method to identify predictors of use over the 12-month study period. A p-value of 0.05 was considered significant for all statistical analyses, which were performed using SPSS version 17.0 (Chicago, IL, USA).

4.3. Results

A total of 216,557 adults met the inclusion criteria for the current analysis, including 84,577 with newly diagnosed depression. Table 4.1 shows that for the overall sample, 61.9% were females and 18.7% were aged 65 years or over on the index date. Regarding baseline comorbidities, 26.9% of the sample had CVD. Comorbid PPS rates were particularly high for both the overall sample and the subsample of individuals with newly diagnosed depression. At the index visit, 45.6% of the overall

sample was prescribed selective serotonin reuptake inhibitors (SSRIs) and 8.6% prescribed SNRIs. Only 3.1% of patients received other newer antidepressants (bupropion and mirtazapine) at the index visit.

Patients with newly diagnosed depression tended to be younger and a greater proportion were females compared to those with non-newly diagnosed depression. They also had lower rates of comorbid physical/mental illnesses and lower prevalence of PPS. Health service utilisation at baseline was lower for those with newly diagnosed depression and a higher proportion were prescribed newer generation antidepressants.

Table 4.1. Sociodemographic and clinical characteristics of the overall sample and comparisons between newly diagnosed and non-newly diagnosed depression*

	The overall sample (n=216,557)	Newly diagnosed depression (n=84,577)	Non-newly diagnosed depression (n=131,980)
Age [mean (SD)]	47.4 (17.0)	43.9 (17.0)	49.7 (16.6)
Age categories [n (%)]			
>=85	1756 (0.8)	637 (0.8)	1119 (0.8)
75-84	13626 (6.3)	4058 (4.8)	9568 (7.2)
65-74	25019 (11.6)	7267 (8.6)	17752 (13.5)
55-64	27438 (12.7)	8787 (10.4)	18651 (14.1)
45-54	44252 (20.4)	15520 (18.4)	28732 (21.8)
35-44	46692 (21.6)	18115 (21.4)	28577 (21.7)
25-34	36338 (16.8)	17740 (21.0)	18598 (14.1)
18-24	21436 (9.9)	12453 (14.7)	8983 (6.8)
Sex [n (%)]			
Male	82,414 (38.1)	30683 (36.3)	51731 (39.2)
Female	134,143 (61.9)	53894 (63.7)	80249 (60.8)
Depression diagnosis at index visit [n (%)]			
Major depression	78296 (36.2)	27029 (32.0)	51267 (38.8)
Other depression	138261 (63.8)	57548 (68.0)	80713 (61.2)

Baseline physical illnesses [n (%)]			
Cardiovascular disease	58350 (26.9)	18132 (21.4)	40218 (30.5)
Diabetes mellitus	23563 (10.9)	7198 (8.5)	16365 (12.4)
Chronic obstructive pulmonary disease	32898 (15.2)	10886 (12.9)	22012 (16.7)
Hyperlipidemia	23249 (10.7)	7351 (8.7)	15898 (12.0)
Hypertension	51271 (23.7)	15596 (18.4)	35675 (27.0)
Renal disease	11854 (5.5)	3766 (4.5)	8088 (6.1)
Cancer	8864 (4.1)	2850 (3.4)	6014 (4.6)
Baseline painful physical symptoms [n (%)]			
Musculoskeletal	99,455 (45.9)	36168 (42.8)	63287 (48.0)
Back	69,981 (32.3)	25036 (29.6)	44945 (34.1)
Gastrointestinal	111,271 (51.4)	40018 (47.3)	71253 (54.0)
Headache/migraine/dizziness	88,164 (40.7)	29996 (35.5)	58168 (44.1)
Baseline mental illnesses [n (%)]			
Schizophrenia	8207 (3.8)	1538 (1.8)	6669 (5.1)
Other psychotic disorder	4650 (2.1)	775 (0.9)	3875 (2.9)
Substance related	6127 (2.8)	1081 (1.3)	5046 (3.8)
Alcohol related	1748 (0.8)	254 (0.3)	1494 (1.1)
Drugs related	1084 (0.5)	196 (0.2)	888 (0.7)
Bipolar spectrum disorder	3882 (1.8)	457 (0.5)	3425 (2.6)
Dementia	7356 (3.4)	1426 (1.7)	5930 (4.5)
Generalised anxiety disorder	11718 (5.4)	2313 (2.7)	9405 (7.1)

Obsessive-compulsive disorder	3797 (1.8)	180 (0.2)	3617 (2.7)
Panic disorder	7388 (3.4)	588 (0.7)	6800 (5.2)
Phobic disorder	1742 (0.8)	131 (0.2)	1611 (1.2)
Post-traumatic stress disorder	404 (0.2)	20 (0.0)	384 (0.3)
Sleep disorder	52001 (24.0)	15196 (18.0)	36805 (27.9)
Hyperkinetic syndrome	133 (0.1)	22 (0.0)	111 (0.1)
Baseline healthcare service use			
Number of outpatient visits [mean (SD)]	31.6 (24.8)	23.9 (20.9)	36.5 (25.8)
ER visit [n (%)]	74970 (34.6)	26178 (31.0)	48792 (37.0)
Hospitalisation [n (%)]	45397 (21.0)	13576 (16.1)	31821 (24.1)
Total 12-month costs prior to index date [mean (SD)]	2268 (3981)	1486 (3469)	2769 (4201)
Index AD [n (%)]			
SSRI	98791 (45.6)	42476 (50.2)	56315 (42.7)
SNRI	18520 (8.6)	7549 (8.9)	10971 (8.3)
Other newer AD	6759 (3.1)	3104 (3.7)	3655 (2.8)
TCA	18787 (8.7)	5873 (6.9)	12914 (9.8)
Flupentixol/melitracen	11449 (5.3)	4341 (5.1)	7108 (5.4)
Other older AD	40897 (18.9)	14016 (16.6)	26881 (20.4)
Multiple AD	21354 (9.9)	7218 (8.5)	14136 (10.7)

Baseline characteristics were measured over the 12-month pre-index period.

Baseline costs were expressed in 2002-3 international dollars.

SD=standard deviation; AD=antidepressant; SSRI=selective serotonin reuptake inhibitor; SNRI=serotonin norepinephrine reuptake inhibitor; TCA=tricyclic antidepressant; other newer AD: bupropion and mirtazapine; other older AD: maprotiline, moclobemide, and trazodone.

*All comparisons between newly diagnosed and non-newly diagnosed depression were statistically significant with a $p< 0.001$ (chi-squared test was used for categorical variables and independent t-test for continuous variables).

Table 4.2. Sociodemographic and clinical characteristics of the overall sample by index antidepressant categories*

Characteristics	SSRI (n=98,791)	SNRI (n=18,520)	TCA (n=18,787)	Flupentixol/ melitracen (n=11,449)	Other newer AD (n=6,759)	Other older AD (n=40,897)	Multiple ADs (n=21,354)
Age [mean (SD)]	45.9 (17.4)	43.8 (16.2)	52.8 (16.1)	50.9 (15.9)	44.1 (16.1)	50.3 (16.6)	46.3 (16.0)
Sex [n (%)]							
Male	36161 (36.6)	6579 (35.5)	7332 (39.0)	3834 (33.5)	2719 (40.2)	17780 (43.5)	8009 (37.5)
Female	62630 (63.4)	11941 (64.5)	11455 (61.0)	7615 (66.5)	4040 (59.8)	23117 (56.5)	13345 (62.5)
Depression diagnosis at index visit [n (%)]							
Major depression	41662 (42.2)	8586 (46.4)	4753 (25.3)	1425 (12.4)	3118 (46.1)	9667 (23.6)	9085 (42.5)
Other depression	57129 (57.8)	9934 (53.6)	14034 (74.7)	10024 (87.6)	3641 (53.9)	31230 (76.4)	12269 (57.5)
Past treatment history [n (%)]							
Newly diagnosed depression	42476 (43.0)	7549 (40.8)	5873 (31.3)	4341 (37.9)	3104 (45.9)	14016 (34.3)	7218 (33.8)
Non-newly diagnosed depression with history of both AD treatment and depression diagnosis	7870 (8.0)	1942 (10.5)	1895 (10.1)	922 (8.1)	685 (10.1)	4127 (10.1)	2600 (12.2)
Non-newly diagnosed depression with history of either AD treatment or	48445 (49.0)	9029 (48.8)	11019 (58.7)	6186 (54.0)	2970 (43.9)	22754 (55.6)	11534 (54.0)

depression diagnosis							
Baseline physical illnesses [n (%)]							
Cardiovascular disease	25424 (25.7)	4328 (23.4)	6044 (32.2)	3821 (33.4)	1560 (23.1)	11876 (29.0)	5297 (24.8)
Diabetes mellitus	9918 (10.0)	1631 (8.8)	2633 (14.0)	1414 (12.4)	661 (9.8)	5128 (12.5)	2178 (10.2)
Chronic obstructive pulmonary disease	14571 (14.7)	2524 (13.6)	3236 (17.2)	1824 (15.9)	900 (13.3)	6709 (16.4)	3134 (14.7)
Hyperlipidemia	9970 (10.1)	1790 (9.7)	2398 (12.8)	1533 (13.4)	637 (9.4)	4706 (11.5)	2215 (10.4)
Hypertension	21667 (21.9)	3431 (18.5)	5746 (30.6)	3576 (31.2)	1293 (19.1)	11006 (26.9)	4552 (21.3)
Renal disease	5142 (5.2)	809 (4.4)	1264 (6.7)	662 (5.8)	367 (5.4)	2548 (6.2)	1062 (5.0)
Cancer	4051 (4.1)	655 (3.5)	865 (4.6)	397 (3.5)	353 (5.2)	1716 (4.2)	827 (3.9)
Baseline painful physical symptoms [n (%)]							
Musculoskeletal	43558 (44.1)	8026 (43.3)	9582 (51.0)	5943 (51.9)	2957 (43.7)	19567 (47.8)	9822 (46.0)
Back	29924 (30.3)	5521 (29.8)	7075 (37.7)	4226 (36.9)	2028 (30.0)	14205 (34.7)	7002 (32.8)
Gastrointestinal	49242 (49.8)	9307 (50.3)	10295 (54.8)	6464 (56.5)	3474 (51.4)	21387 (52.3)	11102 (52.0)
Headache/migraine/ or dizziness	38134 (38.6)	7284 (29.3)	8582 (45.7)	5672 (49.5)	2449 (36.2)	17474 (42.7)	8569 (40.1)
Baseline mental illnesses [n (%)]							
Schizophrenia	3562 (3.6)	645 (3.5)	598 (3.2)	424 (3.7)	259 (3.8)	2030 (5.0)	689 (3.2)
Other psychotic disorder	2015 (2.0)	440 (2.4)	348 (1.9)	196 (1.7)	143 (2.1)	1033 (2.5)	475 (2.2)

Substance related	1854 (1.8)	448 (2.4)	472 (2.5)	133 (1.2)	359 (5.3)	1904 (4.7)	957 (4.5)
Alcohol related	513 (0.5)	83 (0.4)	120 (0.6)	40 (0.3)	93 (1.4)	651 (1.6)	248 (1.2)
Drugs related	308 (0.3)	82 (0.4)	87 (0.5)	50 (0.4)	58 (0.9)	354 (0.9)	145 (0.7)
Bipolar spectrum disorder	1628 (1.6)	400 (2.2)	297 (1.6)	158 (1.4)	158 (2.3)	708 (1.7)	533 (2.5)
Dementia	3301 (3.3)	546 (2.9)	629 (3.3)	367 (3.2)	146 (2.2)	1775 (4.3)	592 (2.8)
Generalised anxiety disorder	4617 (4.70	1007 (5.4)	1305 (6.9)	825 (7.2)	426 (6.3)	2281 (5.6)	1257 (5.9)
Obsessive-compulsive disorder	2351 (2.4)	322 (1.7)	232 (1.2)	144 (1.3)	76 (1.1)	249 (0.6)	423 (2.0)
Panic disorder	3936 (4.0)	715 (3.9)	541 (2.9)	279 (2.4)	185 (2.7)	966 (2.4)	766 (3.6)
Phobic disorder	995 (1.0)	165 (0.9)	92 (0.5)	57 (0.5)	44 (0.7)	236 (0.6)	153 (0.7)
Post-traumatic stress disorder	224 (0.2)	37 (0.2)	16 (0.1)	10 (0.1)	5 (0.1)	53 (0.1)	59 (0.3)
Sleep disorder	20028 (20.3)	3712 (20.0)	5227 (27.8)	2903 (25.4)	1852 (27.4)	12403 (30.3)	5876 (27.5)
Hyperkinetic syndrome	79 (0.1)	22 (0.1)	4 (0.0)	1 (0.0)	8 (0.1)	10 (0.0)	9 (0.0)
Baseline healthcare service use							
Number of outpatient visits [mean (SD)]	30.0 (23.6)	29.8 (23.4)	36.2 (27.4)	32.1 (23.7)	29.3 (23.0)	34.0 (26.5)	32.6 (25.6)
ER visit [n (%)]	33640 (34.1)	6756 (36.5)	5996 (31.9)	3571 (31.2)	2788 (41.2)	14082 (34.4)	8137 (38.1)
Hospitalisation [n (%)]	19842 (20.1)	3824 (20.6)	3883 (20.7)	2062 (18.0)	1688 (25.0)	9188 (22.5)	4910 (23.0)

Total 12-month costs prior to index date [mean (SD)]	2161 (3949)	2198 (3621)	2287 (3931)	1805 (2858)	2448 (4703)	2351 (3966)	2489 (4129)

Baseline characteristics were measured over the 12-month pre-index period.

Baseline costs were expressed in 2002-3 international dollars.

SD=standard deviation; AD=antidepressant; SSRI=selective serotonin reuptake inhibitor; SNRI=serotonin norepinephrine reuptake inhibitor; TCA=tricyclic antidepressant; other newer AD: bupropion and mirtazapine; other older AD: maprotiline, moclobemide, and trazodone.

*All comparisons between index antidepressant categories were statistically significant with a $p < 0.001$ (chi-squared test was used for categorical variables and independent t-test for continuous variables).

Table 4.3. Healthcare costs over the 12-month study period by index antidepressant categories

	SSRI (n=98,791)	SNRI (n=18,520)	TCA (n=18,787)	Flupentixol/melitracen (n=11,449)	Other newer AD (n=6,759)	Other older AD (n=40,897)	Multiple ADs (n=21,354)
Total	2773 (5441)	2974 (4919)	2838 (5558)	2355 (4557)	3160 (5433)	2979 (7504)	3280 (5517)
Psychiatric	833 (1770)	1239 (2262)	511 (1508)	404 (1441)	1177 (2197)	678 (1959)	1252 (2362)
Non-psychiatric	1941 (5183))	1735 (4409)	2327 (5373)	1951 (4345)	1983 (4991)	2301 (7281)	2028 (5033)

12-months costs were expressed in 2003-4 international dollars.

Table 4.4. Service use and healthcare costs over the 12-month study period, overall sample

Service use		
	n (% using)	mean (SD)
Psychiatric outpatient	184271 (85.1)	7.30 (7.72)
Psychiatric inpatient	10916 (5.0)	0.08 (0.46)
Psychiatric emergency	3515 (1.6)	0.03 (0.42)
Non-psychiatric outpatient	212327 (98.0)	27.48 (25.51)
Non-psychiatric inpatient	39077 (18.0)	0.33 (0.98)
Non-psychiatric emergency	70812 (32.7)	0.76 (3.13)
Healthcare costs (international dollars, year 2003-4 values)		
	Mean (SD)	
Psychiatric outpatient	592 (774)	
Psychiatric inpatient	246 (1649)	
Psychiatric emergency	1 (16)	
Non-psychiatric outpatient	1236 (3201)	
Non-psychiatric inpatient	726 (4025)	
Non-psychiatric emergency	74 (286)	
Total	2875 (5827)	

Table 4.5. Univariate analysis of total healthcare costs over the 12-month study period

	B	Sig.
Age (year)	39.12	<.001
Sex		
Male	404.77	<.001
Female	0	
Depression diagnosis at index visit		
Major depression	326.15	<.001
Other depression	0	
Past treatment history		
Newly diagnosed depression	-341.49	<.001
Non-newly diagnosed depression with history of both	1329.20	<.001
AD treatment and depression diagnosis		
Non-newly diagnosed depression with history of either	0	
AD treatment or depression diagnosis		
Baseline physical illnesses		
Cardiovascular disease	1342.73	<.001
Diabetes mellitus	1651.05	<.001
Chronic obstructive pulmonary disease	1045.95	<.001
Hyperlipidemia	785.43	<.001
Hypertension	1393.17	<.001
Renal disease	3224.30	<.001
Cancer	2293.20	<.001

Baseline painful physical symptoms		
Musculoskeletal	550.74	<.001
Back	502.65	<.001
Gastrointestinal	485.40	<.001
Headache/migraine/dizziness	358.87	<.001
Baseline mental illnesses		
Schizophrenia	1377.86	<.001
Other psychotic disorder	983.00	<.001
Substance related	1180.10	<.001
Alcohol related	2404.29	<.001
Drugs related	1075.19	<.001
Bipolar spectrum disorder	1199.70	<.001
Dementia	2265.97	<.001
Generalised anxiety disorder	7.78	.815
Obsessive-compulsive disorder	-26.97	.639
Panic disorder	-117.85	.005
Phobic disorder	-303.70	<.001
Post-traumatic stress disorder	490.78	.005
Sleep disorder	431.28	<.001
Hyperkinetic syndrome	-511.24	.093
Index AD [n (%)]		
Other newer AD	232.75	<.001
Flupentixol/melitracen	-251.85	<.001

Other older AD	123.81	<.001
SNRI	120.89	<.001
TCA	39.14	.161
Multiple AD	304.94	<.001
SSRI	0	
Total 12-month costs prior to index date (1000 international dollars)	.725	<.001

Table 4.6. Univariate analysis of psychiatric healthcare costs over the 12-month study period

	B	Sig.
Age (year)	-4.30	<.001
Sex		
Male	142.18	<.001
Female	0	
Depression diagnosis at index visit		
Major depression	292.82	<.001
Other depression	0	
Past treatment history		
Newly diagnosed depression	-202.70	<.001
Non-newly diagnosed depression with history of both	541.35	<.001
AD treatment and depression diagnosis		
Non-newly diagnosed depression with history of either	0	
AD treatment or depression diagnosis		
Baseline physical illnesses		
Cardiovascular disease	-54.22	<.001
Diabetes mellitus	-26.93	.001
Chronic obstructive pulmonary disease	-9.35	.175
Hyperlipidemia	-47.68	<.001
Hypertension	-81.32	<.001
Renal disease	-60.24	<.001
Cancer	-69.01	<.001

Baseline painful physical symptoms		
Musculoskeletal	-44.88	<.001
Back	-61.90	<.001
Gastrointestinal	-35.22	<.001
Headache/migraine/dizziness	-35.43	<.001
Baseline mental illnesses		
Schizophrenia	1665.72	<.001
Other psychotic disorder	777.27	<.001
Substance related	801.99	<.001
Alcohol related	1321.03	<.001
Drugs related	882.91	<.001
Bipolar spectrum disorder	1098.95	<.001
Dementia	261.25	<.001
Generalised anxiety disorder	6.43	.557
Obsessive-compulsive disorder	487.84	<.001
Panic disorder	160.24	<.001
Phobic disorder	171.68	<.001
Post-traumatic stress disorder	492.45	<.001
Sleep disorder	11.15	.054
Hyperkinetic syndrome	205.40	.040
Index AD [n (%)]		
Other newer AD	207.15	<.001
Flupentixol/melitracen	-257.87	<.001

Other older AD	-92.87	<.001
SNRI	244.87	<.001
TCA	-193.34	<.001
Multiple AD	252.40	<.001
SSRI	0	
Total 12-month costs prior to index date (1000 international dollars)	.066	<.001

Table 4.7. Multivariable analysis (GLM) of total healthcare costs over the 12-month study period

	RR (95% CI)	
	The overall sample (n=216,557)	Newly diagnosed depression (n=84,577)
Age	1.011 (1.011, 1.011)	1.013 (1.013, 1.014)
Sex		
Male	1.143 (1.134, 1.152)	1.231 (1.215, 1.247)
Female	1	1
Depression diagnosis at index visit		
Major depression	1.134 (1.125, 1.143)	1.160 (1.144, 1.176)
Other depression	1	1
Past treatment history		
Newly diagnosed depression	0.959 (0.952, 0.967)	--
Non-newly diagnosed depression with history of both AD treatment and depression diagnosis	1.136 (1.121, 1.151)	--
Non-newly diagnosed depression with history of either AD treatment or depression diagnosis	1	--

Index AD treatment			
	SNRI	1.160 (1.144, 1.176)	1.144 (1.118, 1.170)
	Other newer AD	1.142 (1.118, 1.166)	1.152 (1.114, 1.192)
	TCA	0.905 (0.893, 0.918)	0.895 (0.872, 0.918)
	Other older AD	0.956 (0.946, 0.965)	0.978 (0.960, 0.996)
	Flupentixol/melitracen	0.876 (0.862, 0.891)	0.902 (0.876, 0.929)
	Use of multiple ADs	1.177 (1.162, 1.192)	1.217 (1.189, 1.246)
	SSRI	1	1
Baseline physical illnesses			
Cardiovascular disease			
	Yes vs. No	1.180 (1.169, 1.191)	1.270 (1.248, 1.293)
Diabetes mellitus			
	Yes vs. No	1.256 (1.240, 1.271)	1.315 (1.284, 1.347)
Chronic obstructive pulmonary disease			
	Yes vs. No	1.122 (1.111, 1.134)	1.126 (1.104, 1.148)
Renal disease			
	Yes vs. No	1.161 (1.142, 1.181)	1.230 (1.190, 1.270)
Cancer			
	Yes vs. No	1.326 (1.302, 1.351)	1.478 (1.426, 1.532)
Baseline painful physical symptoms			
Musculoskeletal			
	Yes vs. No	1.068 (1.060, 1.077)	1.069 (1.054, 1.084)
Back			

	Yes vs. No	1.062 (1.053, 1.071)	1.069 (1.053, 1.085)
Gastrointestinal			
	Yes vs. No	1.067 (1.059, 1.075)	1.059 (1.045, 1.073)
Headache/migraine/dizziness			
	Yes vs. No	1.049 (1.040, 1.057)	1.046 (1.032, 1.061)
Baseline mental illnesses			
Schizophrenia			
	Yes vs. No	1.890 (1.854, 1.927)	2.456 (2.342, 2.575)
Other psychotic disorder			
	Yes vs. No	1.185 (1.156, 1.215)	1.368 (1.281, 1.461)
Substance related			
	Yes vs. No	1.301 (1.271, 1.331)	1.323 (1.249, 1.401)
Alcohol related			
	Yes vs. No	1.484 (1.423, 1.548)	1.662 (1.480, 1.867)
Drugs related			
	Yes vs. No	1.188 (1.128, 1.251)	1.483 (1.301, 1.690)
Bipolar spectrum disorder			
	Yes vs. No	1.233 (1.199, 1.267)	1.301 (1.194, 1.417)
Dementia			
	Yes vs. No	1.281 (1.255, 1.308)	1.355 (1.289, 1.424)
Generalised anxiety disorder			
	Yes vs. No	0.998 (0.982, 1.014)	0.996 (0.958, 1.035)
Obsessive-compulsive disorder			

	Yes vs. No	1.069 (1.039, 1.099)	0.978 (0.854, 1.120)
Panic disorder			
	Yes vs. No	0.961 (0.941, 0.980)	1.040 (0.964, 1.121)
Post-traumatic stress disorder			
	Yes vs. No	1.190 (1.094, 1.293)	0.983 (0.655, 1.476)
Total 12-month costs prior to index date (1000 international dollars)		1.182 (1.179, 1.185)	1.175 (1.170, 1.181)

RR=relative risk; CI=confidence interval; AD=antidepressant; SNRI=serotonin norepinephrine reuptake inhibitor; TCA=tricyclic antidepressant; SSRI=selective serotonin reuptake inhibitor; other newer AD: bupropion and mirtazapine; other older AD: maprotiline, moclobemide, and trazodone.

Table 4.8. Multivariable analysis (GLM) of non-psychiatric costs and psychiatric costs over the 12-month study period, overall sample

	RR (95% CI)	
	Non-psychiatric healthcare costs	Psychiatric healthcare costs
Age	1.019 (1.019, 1.020)	0.998 (0.997, 0.998)
Sex		
Male	1.073 (1.063, 1.082)	1.214 (1.201, 1.226)
Female	1	1
Depression diagnosis at index visit		
Major depression	0.978 (0.969, 0.987)	1.363 (1.349, 1.377)
Other depression	1	1
Past treatment history		
Newly diagnosed depression	1.110 (1.100, 1.121)	0.696 (0.689, 0.704)
Non-newly diagnosed depression with history of both AD treatment and depression diagnosis	1.076 (1.060, 1.093)	1.359 (1.334, 1.385)
Non-newly diagnosed depression with history of either AD treatment or depression diagnosis	1	1
Index AD treatment		
SNRI	0.995 (0.979, 1.011)	1.396 (1.372, 1.421)
Other newer AD	1.014 (0.988, 1.040)	1.323 (1.288, 1.360)

	TCA	1.046 (1.029, 1.063)	0.709 (0.695, 0.723)
	Other older AD	1.063 (1.051, 1.076)	0.841 (0.829, 0.853)
	Flupentixol/melitracen	1.031 (1.011, 1.052)	0.681 (0.664, 0.699)
	Use of multiple ADs	1.070 (1.054, 1.086)	1.434 (1.409, 1.458)
	SSRI	1	1
Baseline physical illnesses			
Cardiovascular disease			
	Yes vs. No	1.252 (1.238, 1.266)	1.015 (1.002, 1.029)
Diabetes mellitus			
	Yes vs. No	1.362 (1.343, 1.382)	0.991 (0.974, 1.009)
Chronic obstructive pulmonary disease			
	Yes vs. No	1.168 (1.153, 1.182)	1.004 (0.990, 1.019)
Renal disease			
	Yes vs. No	1.245 (1.220, 1.270)	0.855 (0.835, 0.876)
Cancer			
	Yes vs. No	1.562 (1.528, 1.597)	0.857 (0.835, 0.880)
Baseline painful physical symptoms			
Musculoskeletal			
	Yes vs. No	1.132 (1.121, 1.143)	0.974 (0.963, 0.984)
Back			
	Yes vs. No	1.120 (1.109, 1.131)	0.971 (0.960, 0.982)
Gastrointestinal			
	Yes vs. No	1.163 (1.153, 1.174)	0.955 (0.945, 0.965)

Headache/migraine/dizziness			
	Yes vs. No	1.088 (1.078, 1.098)	1.033 (1.022, 1.044)
Baseline mental illnesses			
Schizophrenia			
	Yes vs. No	0.892 (0.871, 0.931)	3.443 (3.358, 3.531)
Other psychotic disorder			
	Yes vs. No	0.966 (0.937, 0.996)	1.514 (1.465, 1.565)
Substance related			
	Yes vs. No	1.335 (1.298, 1.372)	1.323 (1.282, 1.364)
Alcohol related			
	Yes vs. No	1.467 (1.395, 1.544)	1.707 (1.614, 1.805)
Drugs related			
	Yes vs. No	1.196 (1.124, 1.273)	1.208 (1.129, 1.292)
Bipolar spectrum disorder			
	Yes vs. No	0.991 (0.958, 1.024)	1.649 (1.590, 1.709)
Dementia			
	Yes vs. No	1.291 (1.260, 1.323)	1.451 (1.407, 1.496)
Generalised anxiety disorder			
	Yes vs. No	1.007 (0.988, 1.026)	1.016 (0.994, 1.038)
Obsessive-compulsive disorder			
	Yes vs. No	0.837 (0.809, 0.865)	1.241 (1.197, 1.286)
Panic disorder			
	Yes vs. No	0.902 (0.881, 0.924)	1.062 (1.034, 1.090)

Post-traumatic stress disorder			
	Yes vs. No	1.045 (0.946, 1.154)	1.229 (1.104, 1.368)
Total 12-month costs prior to index date (1000 international dollars)		1.200 (1.197, 1.203)	1.078 (1.074, 1.082)

RR=relative risk; CI=confidence interval; AD=antidepressant; SNRI=serotonin norepinephrine reuptake inhibitor; TCA=tricyclic antidepressant; SSRI=selective serotonin reuptake inhibitor; other newer AD: bupropion and mirtazapine; other older AD: maprotiline, moclobemide, and trazodone.

Table 4.9. Multivariable logistic analysis for use of psychiatric inpatient and emergency services over the 12-month study period, overall sample

	OR (95% CI)	
	Use of psychiatric inpatient services	Use of psychiatric emergency services
Age	0.974 (0.972, 0.975)	0.949 (0.947, 0.952)
Sex		
Male	1.689 (1.620, 1.762)	1.731 (1.613, 1.858)
Female	1	1
Depression diagnosis at index visit		
Major depression	1.909 (1.830, 1.991)	1.771 (1.650, 1.901)
Other depression	1	1
Past treatment history		
Newly diagnosed depression	1.093 (1.042, 1.147)	1.022 (0.943, 1.108)
Non-newly diagnosed depression with history of both AD treatment and depression diagnosis	2.445 (2.310, 2.588)	1.593 (1.441, 1.762)
Non-newly diagnosed depression with history of either AD treatment or depression diagnosis	1	1

Index AD treatment			
	SNRI	1.385 (1.295, 1.481)	0.736 (0.642, 0.843)
	Other newer AD	1.712 (1.558, 1.880)	1.007 (0.838, 1.209)
	TCA	0.747 (0.680, 0.820)	0.831 (0.708, 0.974)
	Other older AD	0.926 (0.872, 0.984)	1.169 (1.062, 1.287)
	Flupentixol/melitracen	0.601 (0.525, 0.688)	1.300 (1.097, 1.540)
	Use of multiple ADs	1.454 (1.365, 1.549)	1.388 (1.250, 1.543)
	SSRI	1	1
Baseline physical illnesses			
Cardiovascular disease			
	Yes vs. No	1.060 (1.003, 1.120)	1.292 (1.178, 1.417)
Chronic obstructive pulmonary disease			
	Yes vs. No	1.080 (1.017, 1.147)	1.120 (1.010, 1.241)
Renal disease			
	Yes vs. No	0.741 (0.667, 0.824)	--
Cancer			
	Yes vs. No	0.773 (0.685, 0.873)	--
Baseline painful physical symptoms			
Headache/migraine/dizziness			
	Yes vs. No	1.062 (1.016, 1.109)	1.125 (1.046, 1.211)

Baseline mental illnesses			
Schizophrenia			
	Yes vs. No	4.271 (4.010, 4.548)	2.971 (2.688, 3.283)
Other psychotic disorder			
	Yes vs. No	1.776 (1.616, 1.953)	1.594 (1.374, 1.848)
Substance related			
	Yes vs. No	2.277 (2.099, 2.471)	1.982 (1.742, 2.255)
Alcohol related			
	Yes vs. No	3.526 (3.112, 3.995)	2.014 (1.656, 2.449)
Drugs related			
	Yes vs. No	1.257 (1.051, 1.502)	1.328 (1.038, 1.699)
Bipolar spectrum disorder			
	Yes vs. No	2.453 (2.236, 2.691)	2.655 (2.321, 3.037)
Dementia			
	Yes vs. No	1.817 (1.638, 2.015)	1.440 (1.172, 1.770)
Generalised anxiety disorder			
	Yes vs. No	0.840 (0.759, 0.929)	--
Obsessive-compulsive disorder			
	Yes vs. No	0.864 (0.757, 0.987)	1.278 (1.068, 1.529)
Panic disorder			
	Yes vs. No	0.825 (0.736, 0.924)	1.478 (1.271, 1.718)
Total 12-month costs prior to index date (1000 international dollars)		1.059 (1.052, 1.067)	1.033 (1.021, 1.045)

OR=odds ratio; CI=confidence interval; AD=antidepressant; SNRI=serotonin norepinephrine reuptake inhibitor; TCA=tricyclic antidepressant; SSRI=selective serotonin reuptake inhibitor; other newer AD: bupropion and mirtazapine; other older AD: maprotiline, moclobemide, and trazodone.

Service use and costs

Service use data are summarised in Table 4.4. Of the overall sample, 85.1% had used psychiatric outpatient services over the 12-month study period. Over the same period, 5.0% of them had been admitted to psychiatric wards for inpatient treatment and 1.6% had psychiatric emergency attendances. Costs of outpatient contacts (psychiatric and non-psychiatric outpatient services) accounted for 63.6% of total healthcare costs. Psychiatric services accounted for 29.2% of the total and the mean cost for psychiatric services was 840 international dollars.

Total healthcare costs

Table 4.7 reveals that higher total healthcare costs were associated with older age, male gender, an index diagnosis of MDD, non-newly diagnosed depression, and having CVD, DM, COPD, renal disease, cancer or PPS at baseline. Male gender was associated with 14.3% higher healthcare costs compared to female gender. Patients who had a MDD diagnosis had 13.4% higher total healthcare costs than those who had a diagnosis of other depression. For those with comorbid CVD, total costs were 18% higher.

Use of SNRIs, other newer generation antidepressants and use of multiple antidepressants were related to higher costs compared to use of SSRIs at the index date. Lower costs were observed for those using tricyclic antidepressants, flupentixol/melitracen and other older antidepressants (maprotiline, moclobemide, and trazodone). The analysis on the subsample of newly diagnosed depression

revealed similar results to those from the full sample. Regarding the model fit, RMSE of the model for total costs was 1316. The predicted mean total costs were 3197 international dollars, slightly higher than the actual mean cost of 2875 international dollars.

Non-psychiatric healthcare costs

Older age, and male gender were related to higher non-psychiatric costs in the following year (Table 4.8). Compared to patients with history of antidepressant treatment or a diagnosis of depression, those with newly diagnosed depression had higher non-psychiatric costs. An index diagnosis of MDD or a baseline comorbid mental disorder were associated with lower non-psychiatric costs, with the only exceptions being alcohol, substance misuse, multiple drugs-related mental disorders and dementia. The presence of a comorbid physical illness or PPS at baseline was related to higher non-psychiatric costs. The potential implications for above findings will be discussed later in this chapter.

Patients prescribed older antidepressants had higher non-psychiatric costs in the following year compared to those prescribed SSRIs while patients prescribed newer antidepressants such as SNRIs or bupropion/mirtazapine had non-psychiatric costs that did not differ significantly from those prescribed SSRIs. The RMSE of the model was 4380. And the predicted mean of non-psychiatric costs was 2410 international dollars while the actual mean cost was 2035 international dollars.

Psychiatric healthcare costs

As shown in Table 4.8, male gender was associated with higher psychiatric costs in the following year. Not surprisingly, patients having an index diagnosis of MDD had increased costs as did those with baseline comorbid mental disorders. Patients with newly diagnosed depression had lower psychiatric costs compared to those who had been diagnosed prior to the index date, which may be related to lower levels of engagement with psychiatric treatments for these patients. Younger age was shown to be related to higher psychiatric costs.

Use of newer generation antidepressants or multiple antidepressants prescribed on the index date were related to higher psychiatric costs (including all drugs costs) compared to those prescribed SSRIs, while use of older antidepressants was related to lower costs. Among comorbid physical illnesses, CVD was the only one found to be associated with higher psychiatric costs. Among PPS, only pain relating to the central nervous system (CNS), i.e. headache/dizziness/or migraine, were related to higher psychiatric costs. The RMSE of the model was 1074. The predicted mean of psychiatric costs was 958 international dollars and the actual mean was 840 international dollars.

Use of psychiatric emergency and inpatient services

Younger age, male gender, a diagnosis of MDD or certain comorbid mental disorders (e.g. psychotic disorders, alcohol or drug-related mental disorders) were more likely to lead to psychiatric emergency attendances and hospitalisations (Table 4.9). CVD or

COPD was also related to higher odds of using these services as were headache, dizziness or migraine complaints at baseline.

4.4. Discussion

This section has provided new evidence on the associations between antidepressant type, comorbidities, service use, and healthcare costs for patients with depression. Although the nature of the associations differed across cost categories, the multivariable models revealed that age, gender, depression severity, past treatment history, comorbid mental/physical illnesses, PPS, and choice of initial antidepressants were all associated with healthcare costs in the following year. Factors including comorbid CVD and PPS were further explored to understand patterns of variation in psychiatric emergency and inpatient service use over the 12-month study period.

Demographic and clinical characteristics

Although previous studies have suggested that medical costs are higher for women than men (Owens, 2008; Woolhandler and Himmelstein, 2007), this study found a different result; for patients with depressive disorders, and taking into account other influences on costs, male gender was shown to be associated with higher costs for both non-psychiatric and psychiatric healthcare services. A study of elderly patients with psychiatric diagnoses suggested that men had more emergency attendances and had greater inpatient costs than women, which led some investigators to propose that when men eschew regular visits to physicians, it is likely that emergency or inpatient treatment may be required as illness progresses (Husaini et al., 2002). Consistently,

male gender was shown to be associated with increased use of psychiatric emergency and inpatient services in the current analysis. One interpretation of the results is therefore that male patients with depression may enter the healthcare system later in the disease course, by which time their illness is more severe, thus generating higher costs.

As shown in Table 4.8, an index diagnosis of MDD or a baseline comorbidity of some mental disorders were associated with lower non-psychiatric costs. This lower cost (or fewer use) in non-psychiatric services may be due to the fact that mental health problems were clinically more important for these subjects compared to the individuals whose depression might be related to physical illnesses and thus secondary.

Antidepressant choice

The current cost analysis showed that initial choice of antidepressants appears to be associated with total healthcare costs in the following year. Compared to patients prescribed SSRIs, those prescribed older antidepressants had lower total and psychiatric costs, whilst patients prescribed SNRIs, and other newer antidepressants had higher total and psychiatric costs. However, to a large extent these differences may be attributed to physician selection; patients prescribed older antidepressants were more likely to suffer other types of depression, to be older, and to have more PPS and physical comorbidities at baseline. Conversely, patients prescribed newer antidepressants were more likely to have MDD, to be younger, and to have fewer baseline physical comorbidities (Table 4.2). These distinctive characteristics may

suggest the existence of physician selection based on patients' clinical characteristics that unfortunately could not be fully adjusted for in the current analyses.

Patients prescribed SNRIs and other newer antidepressants were similar to those prescribed SSRIs in non-psychiatric costs, whilst patients prescribed TCAs and other older antidepressants generally had higher non-psychiatric costs. These results could be interpreted as showing that there were differences in physical comorbidities between these two groups of depressed patients. A systematic review on previous database analyses has suggested that SSRI users may have higher depression-related service expenditures but lower non-depression-related service expenditures than TCA users (Pan et al., 2012). Along with these findings, the current results suggest that depressed patients prescribed older antidepressants may be different from those prescribed SSRIs, SNRIs, and other newer antidepressants in terms of clinical features of depression and comorbidities.

Comorbid cardiovascular disease

Among the frequently co-occurring physical illnesses considered in this chapter, CVD was the only one shown to be positively associated with both non-psychiatric and psychiatric costs. Depression has been revealed to be an independent risk factor for the future onset, progression, and recurrence of CVD (Carney et al., 1988; Ferketich et al., 2000; Nicholson et al., 2006; Rugulies, 2002; Sesso et al., 1998; Wassertheil-Smoller et al., 2004), which can be mediated both by poor health behaviour and by the pathophysiological correlates of depressive symptoms, e.g. neuroendocrine and inflammatory activation (Frasure-Smith and Lesperance, 2010;

Rozanski et al., 2005). Additionally, individual antidepressants have a wide range of cardiovascular effects which may affect cardiovascular-related morbidity and mortality (Coupland et al., 1997; Taylor, 2008; Vieweg and Wood, 2004). It seems likely that the co-existence of CVD and depression may have an impact on the physical conditions of patients and their non-psychiatric costs.

The presence of comorbid CVD was related to higher odds of using both psychiatric emergency and hospitalisation services (Table 4.9) which was consistent with the finding of increased psychiatric costs in these patients. CVD has been shown to be correlated with certain lifestyles, alcohol consumption, and personality traits (e.g. Type D personality), some of which seem to be highly correlated with use of psychiatric services. For instance, Type D has been conceptualised as a personality trait comprising negative affectivity and social inhibition that often co-occurs with depression in patients with coronary artery disease, and that may inhibit remission of depressive symptoms (Albus et al., 2011; Denollet et al., 2010). Although speculative, the association between the presence of CVD and increased psychiatric service utilisation/expenditure in this study may be understood as being indirectly influenced by these unmeasured and potentially associated factors.

Painful physical symptoms

The relationships between depression and pain are complex with similar brain areas regulating both mood and the affective components of pain (Giesecke et al., 2005). High prevalence of pain complaints has been reported in patients with depression (Bair et al., 2003; Husain et al., 2007; Ohayon and Schatzberg, 2003). The current

results added to this evidence in finding a high percentage of comorbid PPS in patients with newly diagnosed depression, which supports findings from previous studies that pain usually appears before the development of MDD (Ohayon and Schatzberg, 2010). On the other hand, pain complaints have been reported to be associated not only with higher odds of having depressive disorders (Barry et al., 2012), but also with an adverse impact on poor treatment response (Bair et al., 2004). Pain complaints seem to be characteristic of depression that is more severe, as evidenced by higher healthcare utilisation, and higher costs (Gameroff and Olfson, 2006).

As most previous studies were based on highly selective samples and did not consider many comorbidities, it is unclear whether these results can be generalised to larger samples of patients in real-world settings, and to what extent other factors such as comorbid mental/physical illnesses would contribute to the possible association between PPS, healthcare utilisation, and treatment outcome. The current results concurred with previous studies in suggesting that the presence of PPS was associated with higher total healthcare costs in the following year. This remained true for those with newly diagnosed depression. In addition, analyses based on origins of pain complaints found that the co-existence of PPS was generally associated with higher non-psychiatric costs but lower psychiatric costs, with headache being the only exception. Unlike other pain complaints, having headache was associated with higher psychiatric costs and greater odds of using psychiatric emergency and inpatient services. A recent study suggested the existence of differences in separate pain modalities in relation to depression, and that a closer relationship may exist between MDD and neuropathic pain than non-neuropathic pain (Ohayon and Stingl, 2012). It

seems possible that a more direct relationship might exist between depression and pain complaints over the central nervous system than PPS from other somatic systems as the current analyses might suggest.

4.5. Limitations and implications

There are limitations with these analyses and two in particular stand out. Firstly, as service use data contained in the NHIRD relate only to health services financed by the NHI system in Taiwan, the perspective of the current analysis was relatively limited, and it was not possible to assess wider economic impacts. Secondly, although the real-world context and whole-country coverage are strengths, the confounding or selection bias due to the non-randomised study design should always be borne in mind while interpreting the results. RCTs may still be regarded as the gold standard approach for estimating the 'true' effects of treatments on outcomes because the random treatment allocation ensures that treatment status will not be confounded with either measured or unmeasured baseline characteristics. In the current cost analysis, the baseline characteristics differed systematically across antidepressant groups. As stated in Section 4.4, physician selection (perhaps based on the differences in patients' baseline characteristics) was suggested to account for a substantial proportion of the cost differences across antidepressant groups. Therefore, the interpretations of the cost-analysis results regarding antidepressant treatments should be made when taking into considerations the potential confounding effects (Austin, 2011).

In conclusion, the analyses suggest a set of significant correlates of healthcare costs for depressed patients. Male gender and a diagnosis of MDD were significantly

associated with higher total healthcare costs. The baseline comorbidities of CVD and headache were associated not only with higher non-psychiatric but also with higher psychiatric costs; in particular, these comorbidities were related to increased use of psychiatric emergency and inpatient services in the following year.

Chapter 5. Effectiveness and utility measurement

The purpose of this chapter is to identify types of outcome measure (both effectiveness and utility measures) that may be appropriate for an economic evaluation of antidepressant treatments for depression in general and specifically in studies using a database approach. Suitability of effectiveness measures for remission and treatment-free status are discussed and compared and methods available for measuring utility are presented. Finally, the strengths, limitations and potential applications to research based on database analyses of these outcome measures are discussed.

5.1. Outcomes in health care evaluations

In evaluating healthcare interventions, a decision regarding the manner in which change is to be measured is required. Given that an intervention may impact on an individual in different ways, there are frequently a number of potentially relevant outcomes and it is useful to separate them into intermediate outcomes and final outcomes.

While intermediate outcome measures generally tend towards biomedical markers, final outcome measures usually focus on morbidity and mortality. Intermediate outcome measures are particularly useful in evaluations when the final outcome measure cannot be observed within the period of the study. When an intermediate outcome measure is used, decisions regarding the effectiveness of the intervention are made on the basis of theoretical or proven relationships (for example, epidemiological

or biological evidence) between the intermediate and the final outcome. For instance, changes in blood pressure may be used as an intermediate outcome while deaths from cerebrovascular accidents are the final outcome. The choice of an intermediate or final outcome measure is thus a function of the disease characteristics.

Brazier et al. (2007b) have argued that health consequences are frequently multi-dimensional, uncertain and disparate and therefore attempting to capture these complexities in a single effectiveness measure is very difficult. Considering the potential need for multiple outcome measures, Craig et al. (2008) suggest that researchers need to choose a primary outcome measure whilst acknowledging the usefulness of secondary outcome measures. It is also necessary to plan exactly how multiple outcome measures will be dealt with in analyses, particularly when the intervention is expected to have an impact on a range of domains. For example, researchers may argue that scores on the Hamilton Depression Rating Scale (HDRS) be used as a primary outcome measure in a study with patients with depressive disorders and that remission be used as a secondary outcome measure.

Economists argue that economic evaluation should have another purpose: to aid decision-makers in maximising the healthcare benefits from available budgets (although it may be equally important to also focus on the distribution of outcomes across populations). As a result, the measure of outcome should better allow the comparison of interventions across a range of diseases and conditions, which is not possible when every disease area uses a different outcome measure. If a new intervention costs more than the comparator but leads to improvements in outcomes, it is necessary for decision-makers to have a view of how much they are willing to

pay for the improvements in outcomes. It is very difficult for decision-makers to take a view on their willingness to pay for improvements in different outcomes across disease areas. These related arguments have led to a growth in generic outcome measures, and specifically *utility* measures, such as the quality-adjusted life-year (QALY).

The concept of QALYs has been first introduced in a paper on kidney transplants in the 1960s (Klarman et al., 1968). In that paper, the authors noted that the quality of life with a kidney transplant was better than that with dialysis, and this information was used to adjust measures of life expectancy. Sometimes there can be more complicated cases: for example, cancer treatments may cause a QALY loss in the short term in order to achieve a QALY gain in the longer term (Drummond et al., 1997). Although not without controversy, in technology appraisals by agencies including NICE in England/Wales, Pharmaceutical Benefits Advisory Committee (PBAC) in Australia, and Canadian Agency for Drugs and Technologies in Health (CADTH) in Canada, the QALY is often used. In such appraisals, clinical outcome measures are expected to have an impact on both survival or health-related quality of life and should be able to be translated into QALYs for evaluations of cost-effectiveness (NICE, 2008; CADTH, 2013; PBAC, 2013). The concept of QALYs will be discussed in more detail in section 5.7.

5.2. Effectiveness measure for depression treatment

Historically, clinicians or researchers have often assessed the short-term effectiveness of depression treatment according to response rates using different clinical scales. For

instance, antidepressants are typically evaluated in clinical trials using efficacy measures (e.g. the HDRS or the Montgomery-Asberg Depression Rating Scale (MADRS)), and efficacy is usually determined by defined reductions on the scale used, say of 50% (Zajecka, 2003). However, as a chronic and relapsing illness, the long-term outcome for depression remains rather disappointing despite many short-term studies with antidepressants having demonstrated efficacy.

While response often denotes a 50% reduction in depression symptom scores, the term remission refers to the virtual elimination of active depressive symptoms (for example, 17-item Hamilton Depression Rating Scale (HDRS17) scores <=7) (Frank et al., 1991; McIntyre et al., 2002). Over the past decades, it has become increasingly recognised that responding to depression treatment but failing to achieve full remission constitutes an adverse outcome (Anderson et al., 2000; Ballenger, 1999). The consequences of not achieving remission can be serious, leading to greater risk of relapse/recurrence (Judd et al., 2000; Ramana et al., 1995), more frequent depressive episodes and shorter periods between episodes (Judd et al., 2000); it may even result in increased mortality and morbidity (de Groot et al., 2001; Empana et al., 2005; Ickovics et al., 2001). In contrast, treating to remission is shown to be beneficial to long-term outcomes, leading to a reduced risk of relapse and improved psychosocial functioning (Judd et al., 2000; Miller et al., 1998; Thase et al., 1992). Therefore, where possible, the key goal of an intervention for depression treatment should be remission (Kennedy and Foy, 2005).

Although desirable, obstacles remain in the way of achieving remission. Drop-outs from treatments are high. In clinical practice, a large proportion of patients

discontinue antidepressant therapy during the first 30 days (42.4%) and only 27.6% continue antidepressant therapy for more than 90 days (Olfson et al., 2006). Besides, inadequate treatment response is a concern. The typical rates of response across antidepressant trials are 60% to 70% over the study periods, usually lasting several months, while remission rates are much lower, ranging from 30% to 50% (Ferrier, 1999; Rush and Trivedi, 1995). For example, antidepressant response rates in a tertiary, university-affiliated hospital database of 259 patients (with symptoms assessed at 8, 14, 20, and 26 weeks) revealed that only 36% of patients achieved full remission with antidepressant treatment, implying that 64% of patients had unsatisfactory treatment response (Kennedy et al., 2001).

Evidence suggests that there is a window of opportunity for achieving full remission of depression and an increasing duration of depression has a negative impact on the probability of recovery (Keller et al., 1992; Lin et al., 1998). In an observational study of 431 patients treated with MDD, 50% of patients recovered within the first six months (Keller et al., 1992). The likelihood of recovery in subsequent months declined from 15% during the first three months of follow-up to 1% to 2% per month three to five years after the start of the study. Therefore, history of previous episodes or disease duration seems to be an important factor in determining the clinical outcomes of depression.

Failing to achieve full remission of MDD increases the risk of relapse (Judd et al., 1998; Judd et al., 2000; Lin et al., 1998; Paykel et al., 1995). The presence of ongoing subthreshold symptoms suggests that the depressive illness is still active (Judd et al., 1998). Patients with residual subthreshold depressive symptoms have significantly

more severe and chronic courses, with shorter well intervals than asymptomatic patients (Judd et al., 2000). Several studies have reported that the risk of recurrence is three times that of patients without residual symptoms (Judd et al., 1998; Lin et al., 1998; Paykel et al., 1995). Patients with residual symptoms relapsed to their next major depressive episode more than three times faster than asymptomatic patients and to any depressive episode more than five times faster in a naturalistic study that followed up patients (n=237) for at least ten years after treatment (Judd et al., 1998). As a strong predictor of subsequent relapses, researchers have reported that after 15 months of follow up, relapses occurred in 76% of the patients with residual symptoms versus 25% of those without (Paykel, 1998; Paykel et al., 1995).

Furthermore, evidence from a randomised trial in primary care clinics showed there may be potential savings in costs by treating depression to remission (Simon et al., 2000). In a naturalistic study, remitting patients have been reported to have three fewer outpatient visits and 22 fewer sick leave days than non-remitting patients. Health-related quality-of-life scores measured by the EuroQol five dimension (EQ-5D) improved by 40% for remitting patients when compared with non-remitting ones (Sobocki et al., 2006). Although the above findings are all context-specific, remission is likely to have substantial economic benefits, which further strengthens the case of aiming for full remission in the treatment of depression.

5.3. Use of remission as an outcome measure in database studies

Prospective naturalistic studies have been carried out to explore health problems using computerised databases. Compared to clinical trials, use of databases can improve generalisability of findings due to the use of less restrictive inclusion criteria. Database studies are also useful when assessing economic impacts of depression treatment to complement results from randomised trials. The relative completeness of information (albeit from a narrower perspective) in databases can be the best available direct source of cost information particularly when treatment costs are the main concern. Moreover, given the chronic and relapsing nature of depression, the longer-term economic impact of the illness and treatment would be of greater importance than its short-term effects. In this sense, database studies can provide longitudinal information on service use, and hence costs, after the acute and/or even continuation phase of treatment which clinical trials seldom afford.

However, clinical rating scales are usually not available in databases because key data in these databases are prescriptions, pharmacy claims and service use. It is not possible to ascertain the remission defined by clinical rating scales, like the HDRS, in database analyses. As a result, the measurement of longer-term clinical impacts following the outcome of acute phase treatment, e.g. remission/non-remission, cannot be readily generated.

In response to this, the use of 'approximate definitions' has been proposed. Sicras-Mainar and colleagues described the concordance between remission determined by clinical assessment and a database definition of remission, i.e.

cessation of antidepressant use based on information obtained from computerised prescription databases of patients with major depression (Sicras-Mainar et al., 2010a). In that study, a specialist in psychiatry assessed a random sample of patient histories and determined whether patients were in remission according to clinical criteria, i.e. International Classification of Primary Care (ICPC-2) (Lamberts et al., 1993). Regarding the database definition, patients were considered in remission when they did not receive further prescriptions of antidepressants for at least six months after completing treatment for a new episode. The 4,572 subjects were selected according to the following criteria: 1) over 17 years old, 2) had a major depression episode with a treatment prescribed between January 2003 and March 2007, 3) demonstrated a period of at least six months without depression prior to the major depression episode, 4) prescription followed minimum required treatment criteria, i.e. > 60 days of antidepressant treatment after the first prescription (NICE, 2004), and 5) a follow-up occurred of at least 18 months (12-month study period and another six-month observational period to assign study sub-group). Two sub-groups were considered: patients in remission and patients not in remission. The underlying assumption seems to be that a new episode for depression is defined as having an antidepressant prescription with no prescription in the previous six months (Wade et al., 2007) and from this, it can be derived that if a patient stops treatment and has no new prescription during the following six months, he/she has completed a depression episode. If he/she starts an antidepressant after that, it will be a new episode. While this proxy definition of remission may have its merits for database analyses, there are obviously other reasons for a patient to stop medication, e.g. lack of effectiveness, side effects, or patient-physician communication failures (Demyttenaere, 1997; Johnson, 1981). Therefore, modifications may be needed in applying this proxy

definition to analyses which will be discussed later in this chapter. The concordance between remission by approximation and remission according to clinical criteria in Sicras-Mainar et al (2010) is detailed in Table 5.1.

Table 5.1. Validity of remission by approximation from Sicras-Mainar et al. (2010)

Validation Method	**Reference Criteria**	
Remission by Approximation	**Clinical Histories**	
N = 133	**Positive**	**Negative**
Positive	74	5
Negative	6	48
Statistics	Value (%)	95% CI
Validity of the measurement		
Sensitivity	92.5	88.0 - 96.9
Specificity	90.6	85.6 - 95.6
Positive predictive value	93.7	89.6 - 97.8
Negative predictive value	88.9	83.6 - 94.2
False positives	7.5	3.0 - 11.9
False negatives	9.4	4.4 - 14.4
Reliability		
Cronbach's alpha	90.6	85.6 - 95.6
Area under the curve	91.2	86.5 - 96.1
Concordance		
McNemar test	58.1	49.7 - 66.5
Pearson correlation	82.8	73.1 - 92.5
Weighted kappa (Cohen)	82.8	73.1 - 92.6
Clinical utility		
Positive Probability Ratio	9.8	—
Negative Probability Ratio	0.1	—

Reference criteria: Review of patients' histories. Significance: $p < .001$ in all cases. CI: confidence intervals (adapted from Sicras-Mainar et al. 2010) (Sicras-Mainar et al., 2010a)

This database definition of remission has been employed in another economic evaluation study (Byford et al., 2011) in which 12-month costs were compared between remitters and non-remitters. Costs were significantly lower for patients who experienced remission after the acute treatment phase than for those with less favourable outcomes, and total costs fell over time at a faster rate for remitters compared to non-remitters. Nevertheless, this approximate definition can cause several problems. There may be other motives for discontinuing the prescription other than the patient being in remission (lack of effectiveness or adverse side effects etc.). On the other hand, persistence of treatment with antidepressants should not always be interpreted as absence of remission, as it is recommended that patients be maintained on medications after achieving remission, and for a longer period in selected patients at risk of relapse (Kupfer, 1991). Limitations of this database definition of remission and its potential application will be discussed in the next section.

5.4. Limitations and modifications of the database definition of remission and consideration of 'treatment-free status'

The justification for the above-mentioned database definition of remission is based on its comparison with the clinical criteria by a chart review of patients from six primary care centres in Spain. In their discussion, the authors suggested 'caution in generalising the results' (Sicras-Mainar et al., 2010a). Indeed, the generalisability is questionable when applied to other populations, e.g. in Taiwan. Moreover, in the above study, the authors provide data on the internal consistency of treatment cessation in relation to clinical remission. The validity of this approach to determining remission could be still invalid as other measures should have been used for assessing

its reliability and predictive ability. Taking into consideration both the strengths and limitations, it may be better to interpret this definition of remission in other ways to avoid confusion with actual remission defined by clinical rating scales.

In the analyses presented in this thesis, a more descriptive term 'treatment-free status' is thus used instead of 'remission' (Pan et al., 2013c). Meanwhile, 'late re-contact' is used instead of 'relapse/recurrence'. In recent research using the same database definition, 'sustained treatment-free status' was further defined which required no re-start of antidepressant treatments (late re-contacts) through the 18-months follow-up period (Pan et al., 2013c). The 'sustained treatment-free status' was shown to be associated with early attrition and also to impact long-term treatment costs as shown in Chapter 6 of this thesis (Pan et al., 2013a). While acknowledging the limitations of this database definition, the term 'sustained treatment-free status' seems likely to indicate initial treatment effectiveness without later clinical fluctuations sufficient to trigger a medical contact while simultaneously specifying another subgroup of subjects who have later re-contacts which may reflect changes in clinical conditions such that help-seeking is considered beneficial.

Since the National Health Insurance Research Database (NHIRD) in Taiwan did not provide direct clinical information, diagnostic accuracy, severity of depression and treatment response could not be definitively ascertained in this thesis. The use of 'sustained treatment-free status' instead of remission in this thesis may therefore make any conclusion about remission, relapse or clinical outcome more challenging to make. Clinical visits might be triggered and/or maintained by clinical contingencies, as well as other factors pertinent to help-seeking behaviours, and so 'sustained treatment-free

status' and 'late re-contact' are not *equivalent* to clinical outcomes although they may be considered as *proxies* for such effects. Furthermore, regular service attendance does not ensure compliance to prescribed medication. These methodological issues can be difficult to resolve, given the case numbers in a study such as this and the inherent clinical heterogeneity. Through proper sampling and linkage to clinical records, further studies may focus on proper validation of the clinical diagnosis, ascertainment of symptoms and severity, to explore the correspondence and disparity between help-seeking behaviours and clinical outcomes.

5.5. Utility/quality weights for health states

In economic evaluations 'utilities' are often used to measure outcomes and are anchored by 0 and 1, where 0 indicates death and 1 indicates full health (Drummond et al., 1997). States worse than death can also be included, with these taking a negative value. Measurement of utility requires health states to be defined and described and then valued. Such valuation can be direct or indirect.

Direct elicitation methods

In direct measurements, the relevant dimensions of health and levels of each dimension are assessed. Examples of these dimensions include physical, social and cognitive function; psychological well-being; and pain. These are incorporated into a health state description for the disease or condition of interest and should be based on direct patient experience, although health professional views and values from the literature can also be used (Whitehead and Ali, 2010). The most well-known

approaches to value health states are the visual analogue scale (VAS), the time trade-off (TTO) and the standard gamble (SG).

The simplest approach to measuring utilities is to ask the individual to rank health states from most preferred to least preferred and to place the states on a scale such that the intervals between placements relate to their preferences (Drummond et al., 1997). The VAS is an example of this approach which involves the use of a scale shown on a single line.

The SG approach is considered the classical method of measuring utilities when uncertainty exists. It was formulated by von Neumann and Morgenstern (1944) who developed a model where they described how a rational individual would make decisions in the face of uncertain outcomes. The SG approach involves presenting the individual with a choice between two alternatives: a health state that is certain and a gamble with one better (full health) and one worse (usually death) outcome possible. The probability of experiencing the worse outcome is varied until the individual is indifferent between the gamble and the health state currently being experienced (or assumed). The probability at that point represents the value of the health state.

The TTO approach requires the individual to consider how much time in full health they would be willing to sacrifice to avoid a certain poorer health state (Burstrom et al., 2006). The individual may be indifferent between a particular health state say of ten years and a shorter lifetime of seven years, resulting in an estimated utility for this health state of 0.7 (seven years divided by ten years).

Indirect elicitation methods

Direct elicitation methods are time consuming and thus rarely used in evaluations. Indirect elicitation methods are seen as a practical alternative in many studies because they involve the use of pre-scored generic preference-based measures. In these standardised measurements, health states are described, which cover a range of general aspects (or dimensions) of health. The EuroQol five dimensions (EQ-5D), the Short Form 6D (SF-6D) (Brazier et al., 2002) and the Health Utilities Index (HUI) (Horsman et al., 2003) are examples. The above measures differ in the dimensions of health that are assessed and the number of levels defined for each dimension. The values derived for each state were obtained from a TTO exercise for the EQ-5D and HUI (Drummond et al., 1997), while the SF-6D was based upon the SG approach (Brazier et al., 2002).

The EQ-5D was found to be the most commonly used generic instrument in cost utility analyses by a previous review (Richardson and Manca, 2004). It has five domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each has three levels: no problems, some problems or severe problems. The 243 possible health states from the EQ-5D have a utility value attached to them. The EQ-5D is short and can be self-completed or used in face-to-face interviews (EuroQol Group, 2013).

Generic instruments may allow comparisons across disease groups, but may be insensitive to particular aspects of certain conditions. This has led to the development of some condition-specific measures such as the Asthma Quality of Life Questionnaire (Haldar et al., 2009) and the Inflammatory Bowel Disease Questionnaire (Dudley-Brown et al., 2009).

Limitations and controversy in valuing utilities

It is noteworthy that various approaches can generate different utility values, even where the same individual is valuing the health states. This can partly be due to differences in the health domains that are assessed as well as the use of different valuation methods. Therefore, the method used to generate utility values should be cautiously considered when applying such values.

5.6. Utility weights (quality weights) and related studies in patients with depressive disorders

Since depression is associated with marked decreases in functioning and health-related quality of life (Hays et al., 1995; Saarijarvi et al., 2002), as well as an increase in disability days (Lecrubier, 2001), it is essential to evaluate economic impacts of depressive disorders while incorporating quality of life data. Additionally, because antidepressant treatments have been shown to be effective in reducing depression severity (Brown et al., 2000; Nierenberg, 2001) and in increasing patient functioning and health-related quality of life (Revicki et al., 1998; Reynolds, 1997), conducting a cost-utility analysis comparing impacts of antidepressant treatments on cost and quality of life seems sensible. Analysis of data from randomised trials found that patients in remission were more likely to maintain paid employment and report fewer days missed from work (Simon et al., 2000). Possibly, depressed patients with different levels of clinical responses may differ in levels of functioning and quality of life as well.

In depressive disorders, a number of studies have evaluated the suitability of the use of

the EQ-5D, which has been applied in various areas as a measure of outcome in studies comparing different treatments (EuroQol Group, 2013). The EQ-5D shows good correlation to clinician rated measures of depressive symptoms severity, e.g. CGI (clinical global impression scale) and BRAMES (Bech-Rafaelsen melancholia scale) (-0.539, -0.576) in patients with depression (Gunther et al., 2008). For patient-rated severity measures such as the Patient Health Questionnaire (PHQ), the correlation is also moderately good (-0.451 to -0.638) (Mann et al., 2009). In terms of responsiveness, the EQ-5D is very responsive to improvement in depressed patients (Caruso et al., 2010; Fernandez et al., 2005; Reed et al., 2009; Sapin et al., 2004; Sobocki et al., 2007; Swan et al., 2004). But the findings from Serfaty et al (2009) suggest that the EQ-5D is less responsive than the BDI-II (Beck depression inventory-II). The patient group in that study had a mean age over 70 years old, suggesting that the EQ-5D might perform worse for older persons with depression.

Using clinical rating scales, depressed patients are usually categorised as responders and remitters (Committee for Proprietary Medicinal Products, 2002). Previous utility studies have also found substantial differences in EQ-5D mean utility between patients identified as in remission versus those who are not (Mann et al., 2009; Sapin et al., 2004). Moreover, as responders sometimes present residual depressive symptoms, 'responder remitters' 'responders non-remitter' and 'non-responders' were further categorised in a study with MDD patients in primary care (Sapin et al., 2004). In that study, the different clinical response profiles, assessed by the MADRS, were also revealed by EQ-5D at endpoint: 0.85 for 'responder remitters', 0.72 for 'responders non-remitter', and 0.58 for 'non-responders'. Considering that the study was conducted in France, it may have been better to use social preference values based on

the French general population. But these values were not available and weights were therefore adopted from a UK study that provided the technical estimates widely used in countries that lack their own reference data (Dolan et al., 1995).

For different countries including the UK, Germany, Japan, and the USA (Dolan, 1997; Greiner et al., 2005; Tsuchiya et al., 2002; Shaw et al., 2005), an index score is available and assigned to all health states described by the EQ-5D according to a set of preference values derived from surveys of the general populations. In depressive disorders, a number of studies have evaluated the suitability of applying the EQ-5D index-UK, derived from preference values of the UK general population (Hayhurst et al., 2006; Lamers et al., 2006; Sapin et al., 2004). For instance, more severe patients with MDD have been demonstrated to have lower scores of EQ-5D index-UK (Sapin et al., 2004). Several other studies showed that the EQ-5D index-UK discriminates between groups with varying levels of depression (Hayhurst et al., 2006; Lamers et al., 2006). Overall, the results demonstrated that the EQ-5D index-UK had medium to large correlations with clinical measurements of depression severity.

Utility values are needed for calculating QALYs in economic evaluations (Gold et al., 1996b; Pyne et al., 1997; Torrance and Feeny, 1989). However, despite of the availability of the Taiwanese valuation set for the EQ-5D health states (Lee et al., 2013), there have been no utility data on the different health states of depression based on the EQ-5D index-Taiwan. Therefore, the utility values from research using the EQ-5D index-UK were applied in the cost-utility analysis described in Chapter 7.

Limitations in the use of quality weights elicited from a different country

The use of the EQ-5D index-UK to assign utility values to Taiwanese patients could have potential problems. People from different countries could differ in the preference values they place on health states (Badia et al., 2001; Johnson et al., 2005). Indeed, these preference values have also been shown to differ between ethnic groups even within a country (Shaw et al., 2007). Despite these limitations, it is not uncommon to apply social preference values elicited from other countries in cost-utility studies due to the lack of well-established data from the country where the study is set. Among the country-specific scores, the EQ-5D index-UK has been widely applied in cost-utility studies in countries other than the UK. For instance, despite the availability of the EQ-5D social tariff from neighbouring Denmark, one Swedish study chose to use the EQ-5D index-UK because it was more established and widely used (Burstrom et al., 2006).

There are other reasons to choose the EQ-5D index-UK rather than index scores from other countries to assign utility values in this thesis. Firstly, compared to other country-specific scores, the EQ-5D index-UK has been widely tested for its suitability in the field of depression research and data on the utility values of different depressive health states using the EQ-5D index-UK are relatively complete. Secondly, despite the availability of the Taiwanese valuation set for EQ-5D health states, there have been no utility data on health states of depression based on this index (Lee et al., 2013). The index in Taiwan was estimated using TTO method (Lee et al., 2013). The rank correlation coefficients and mean absolute differences between estimated quality weights of 243 health states in the Taiwanese sample and those estimated in the UK

(Dolan, 1997), Japan (Tsuchiya et al., 2002) and South Korea (Jo et al., 2008) have been calculated. The magnitude of the mean absolute differences between the Taiwan and the UK weights (0.146) was much smaller than the differences between the Taiwan weights and those from Japan and South Korea (0.422 and 0.592, respectively). Additionally, the rank correlation coefficient of estimated values between the Taiwanese and the UK weights was 0.924, indicating a strong positive correlation, whereas the correlations between the Taiwan weights and those of Japan and South Korea were 0.879 and 0.811, respectively. Therefore, if weights from another country are to be used in this study, then the weights from the UK seem more appropriate compared to those from apparently more similar countries in the same region as Taiwan.

An international comparison of country-specific EQ-5D values for health states has showed the same approximate relative importance of health states across countries (Norman et al., 2009). It seems likely that despite the presence of different preference values for certain health states across countries, the main trend for the rank of health states is similar. Specifically in depressive disorders, a previous study demonstrated that despite the differences in the absolute utility values based on the EQ-5D index-UK and EQ-5D index-Germany, changes in utility values between different health states of depression are very similar for the two country-specific index scores (Günther et al., 2008). In this sense, the adoption of the EQ-5D weights from another country seems to be a viable choice in the proposed cost-utility analyses in this thesis given the focus on the changes in utility values (but not in the absolute values) between health states of patients with depressive disorders.

5.7. Quality-adjusted life-years (QALYs)

In cost utility analysis, QALYs are used as outcome measures and these are derived from the utility values using area-under-the-curve methods (Drummond et al., 1997). Given that the QALY combines information on mortality and morbidity, it is potentially of use for comparing interventions (Kind et al., 2009). However, it has been criticised as being too reductionist (Knapp, 2007). It may account for some aspects of a healthcare intervention but may neglect many others. Other concerns are associated with the fundamental underpinnings of the QALY (Lipscomb et al., 2009). It is for example assumed that the value of being in a health state for two years is twice that of being in the health state for one year (Hauber, 2009). Related to this is the assumption that any combination of time in a health state and utility of that state that gives rise to X QALYs is equivalent. This independence between quantity and quality may not hold. Therefore, although QALYs are potentially powerful measures, we should also be cautious in how they are applied.

5.8. Summary and implications

In this chapter, effectiveness measures for depression treatment were considered within the specific context of the proposed database analyses based on routinely-collected healthcare information in Taiwan. Clinically judged remission is an ideal treatment goal for depression treatment, but it may not be a viable choice in this thesis due to lack of the necessary clinical outcome data. Alternatively, the suitability of a database-derived remission definition was evaluated and then, the usefulness of a modified definition of sustained treatment-free status was considered.

Valuation methods for utilities were summarised with a focus on generic utility instruments. Specific data on utilities of health states for patients with depression were reviewed. Limitations and controversy regarding utilities and valuation methods were discussed as well. Data of utilities for health states of depression are relatively limited. Future research is needed to provide utility values through both direct and indirect elicitation methods, and to explore appropriate methods for linking these to database information such as that in this study.

Chapter 6. Relationship between depression outcomes and subsequent costs

The purpose of this chapter is to assess the longer-term economic impacts of outcome status following initial treatment for depression. Service use and costs for patients with depression for a longer period of follow-up (i.e. three consecutive years) are described. Since the type of depression, past treatment history, comorbid mental/physical illnesses, painful physical symptoms (PPS), and choice of initial antidepressants were found in Chapter 4 to be associated with healthcare costs and service use for patients treated for depression in Taiwan (Pan et al., 2013b), the analyses in this chapter are conducted taking into account the above factors. Specific objectives are to explore factors associated with initial treatment outcome status (sustained treatment-free status, continuous treatment, and late re-contact) and to examine healthcare costs over the following three years by outcome status.

6.1. Introduction

Although the relationship between depression and levels of health service use and costs has been consistently reported (Katon, 2003; Simon et al., 1995), much less is known about how this relationship is influenced by treatment outcomes. Data from longitudinal studies suggest that costs are significantly lower for patients who experience remission after the acute treatment phase than for those with less favourable outcomes (Sicras-Mainar et al., 2010b; Simon et al., 2006; Sobocki et al., 2006). Furthermore, total costs have been shown to fall over time at a faster rate for remitters compared to non-remitters (Byford et al., 2011). However, the existing literature is limited in a number of ways. First, findings have been based on relatively

small samples (Simon et al., 2006; Sobocki et al., 2006). Second, the duration over which study subjects have been followed-up in each study has been limited to six to 12 months; and so the impact of initial treatment outcome status on service use and costs beyond this point is unknown. Third, many of the studies assessed outcome, e.g. remission, at a point when a large proportion of participants were still receiving antidepressants, thus leaving the impact of cessation of antidepressant treatments, which is commonly seen in real-world settings, largely undetermined.

6.2. Methods

Data

Data were extracted from the National Health Insurance Research Database (NHIRD). As stated previously, the index date for the analyses was defined as the date on which the subject was first prescribed with an antidepressant for a diagnosis of depressive disorders in 2003.

Participants

All insured subjects of the NHI system in Taiwan meeting the following criteria were included:

- Age 18 years or over on the index date.
- At least one prescription for an antidepressant for treatment of major depressive disorder (MDD: ICD-9-CM codes: 296.2x, 296.3x) or other depressive disorders

(ICD-9-CM codes: 300.4x, 311.xx) in 2003.

- At least three antidepressant prescriptions within the first three months of the index date (Byford et al., 2011).
- Data available for a minimum of 12 months before the index date and a minimum of 36 months after the index date.

Definition of initial outcome status

In this chapter, proxy criteria for treatment outcomes were operationally defined, which focused on the cessation of antidepressant treatment. This proxy measure has been validated by evaluating the concordance between 'remission' as defined by antidepressant cessation for at least six months and remission determined by clinical criteria; the level of concordance between the two approaches was considered acceptable (Cronbach's alpha 90.6%, 95% CI 85.6, 95.6) (Sicras-Mainar et al., 2010a). The proxy measure of remission was also used in a recent economic evaluation for patients with depression (Byford et al., 2011), a naturalistic, longitudinal study carried out using data from a large primary care UK general practice research database between 2001 and 2006. That study included patients receiving at least three antidepressant prescriptions in the first three months and remission was defined as patients not using antidepressants for at least six months after antidepressant treatment had ended. The results showed that over 12 months from the index prescription, patients classified as non-remitters had more contact with primary care services (17 vs. 13 GP visits) and secondary care psychiatrists and other specialists (47% vs. 40%). Total 12-month costs per participant were significantly lower for remitters.

Despite the usefulness of this proxy definition of remission in previous studies, to prevent confusion from actual remission defined by clinical rating scales, a more descriptive term (treatment-free status) instead of remission was used in this thesis (also see Chapter 5). Additionally, 'sustained treatment-free status' was defined as no re-start of antidepressant treatments (late re-contacts) through the 18-month follow-up period (Pan et al., 2013c). As with Byford et al. (2011), only participants who had at least three antidepressant prescriptions in the first three months were included to ensure that a group of depressed patients with an initial presentation that justifies antidepressant treatment was identified (Byford et al., 2011).

Study participants were therefore grouped according to three treatment outcomes:

(i) Sustained treatment-free status: patients who had antidepressant cessation for at least six months and had not restarted antidepressant use by the end of the 18-month observation period (see below for definition of the 18-month observation period).

(ii) Continuous treatment: patients who had not had cessation of antidepressant use for at least six months by the end of the 18-month observation period.

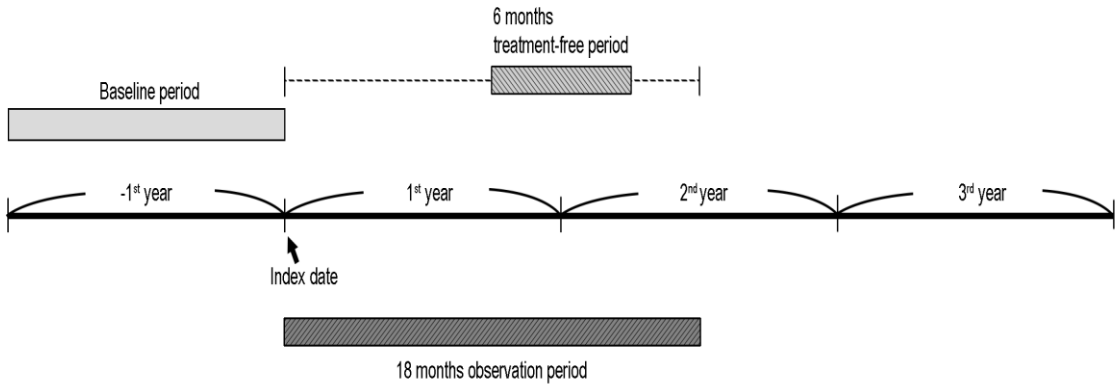
(iii) Late re-contacts: patients who had achieved antidepressant cessation for at least six months but later restarted antidepressant use during the 18-month period of observation.

Observation period for treatment outcome status

For each individual, the observation period started on the index date, and continued for 18 months after this point. The additional six months after the first 12 months was

included to ensure there was adequate time to assess whether treatment-free status had been achieved, given the definition described above. The treatment-free period, i.e. cessation of antidepressant treatment, could begin at any point during the 12 months after the index date (please refer to Figure. 6.1.), but a participant needed to remain off antidepressants for a minimum of six months to meet the definition. Hence, an observation period of 18 months was required.

Figure. 6.1. Diagram for time periods used in the analyses



Demographic and clinical information

Demographic and clinical data, including age, gender, index diagnosis of depressive disorders (MDD vs. other depression), and initial choice of antidepressants were extracted. Provider information (the prescribing physician: psychiatrist vs. non-psychiatrist) and clinical setting at the initial visit (outpatient, emergency or inpatient services) were also extracted. Participants were grouped according to past treatment history: newly diagnosed depression (defined as people who had not received antidepressant treatment or a depression diagnosis in the 12 months before the index date) and non-newly diagnosed depression.

Baseline characteristics were collected regarding comorbid mental disorders, physical illnesses (cardiovascular disease, diabetes mellitus, chronic obstructive pulmonary disease, renal diseases, and cancer), painful physical symptoms (PPS) (headache, backache, musculoskeletal and gastrointestinal pain, and others) (also see Chapter 3, Section 3.2.), as well as healthcare utilisation/expenditure during the 12 months prior to the index visit.

Service use and costs

Service use data extracted from the NHIRD for the three years following the index date included contacts with outpatient services, emergency attendances, and inpatient stays (for all reasons). The percentage of patients with at least one unit of service use and the mean number of service contacts were reported. Annual costs (including all medication costs) were calculated from the actual claims data, were converted by purchasing power parity (PPP) conversion rates (World Economic Outlook (WEO) data, 2013) and expressed in international dollars.

Statistical analyses

Sociodemographic data, clinical characteristics, baseline comorbidities, as well as initial choice of antidepressants were described and compared between groups by initial outcome status. Service use and costs of groups based on these outcomes were also described by service categories and compared for the next three years after the index date.

To identify characteristics predictive of outcome statuses, a multinomial logistic regression analysis was performed, with treatment outcomes as the dependent variables; the independent variables included age, sex, index depression diagnosis, past treatment history, physician specialty, clinical settings at index visit, initial choice of antidepressants, baseline comorbid mental/physical disorders, and baseline PPS.

A multivariable generalised linear model regression with a log link and gamma variance function was employed (McCullagh and Nelder, 1989) to examine the effects of initial treatment outcomes on total healthcare costs while adjusting for other independent factors. Besides the first year model, separate models were separately run for the second year, and third year total healthcare costs to explore the impacts of initial outcome status on total healthcare costs over the longer-term follow-up. Considering potential issues of multiple comparisons, a stringent significance criteria of p-value < 0.01 was adopted for all statistical analyses, which were performed using Stata version 11.1 (StataCorp LP, College Station, TX, USA).

6.3. Results

Besides the inclusion criteria used in Chapter 4, subjects were required to have at least three antidepressant prescriptions within the first three months of the index date to be included in the current analysis. This was to recruit a population of patients whose depressive disorders were initially severe enough to trigger clinical visits with antidepressant treatments and to follow up them for the consecutive three years (also see Section 6.2.). As a result, a total of 126,471 adults met the inclusion criteria. Among them, 43,065 (34.1%) were classified as having achieved sustained

treatment-free status, 71,543 (56.6%) were classified as being continuously on antidepressant treatment, and 11,863 (9.4%) had cessation of antidepressants for six months and late re-contacts during the observation period.

Table 6.1 shows that there were noticeable differences in several demographic and clinical variables between groups by treatment outcomes. The largest difference was noted for past treatment history. Index depression diagnosis and comorbid mental disorders also differed substantially between the groups.

Table 6.2 shows that there were significant differences in the use of various services and costs between the three outcome groups (except for psychiatric emergency services in the first year). These differences remained until the end of the three-year follow-up. Notably, while service use and costs in the first year were relatively comparable between the groups, service use and costs for those who achieved sustained treatment-free status sharply decreased in the second and third years (e.g. 84.6% used psychiatric outpatient services in the first year while only 27.1% and 28.2% used such services in the second and third year respectively) and were much lower than those for the other groups of patients: 87.5% of subjects in the group of late re-contact used psychiatric outpatient services in he first year, 78.4% in the second year and 59.6% in the third year).

Factors associated with treatment outcome status

In Table 6.3, the multinomial logistic regression shows that patients who achieved sustained treatment-free status tended to be younger than those who were on

continuous treatment. Younger age was also predictive of having late re-contacts. Females were more likely to have late re-contacts than being on continuous treatment. Patients who had MDD were more likely to be continuously on antidepressant treatment. Newly diagnosed depression was associated with sustained treatment-free status and late re-contact, rather than being on continuous treatment. Patients with a history of both antidepressant treatment and a diagnosis of depression were the most likely to be on continuous treatment. Physician specialty at the index visit was associated with sustained treatment-free status and being diagnosed and prescribed antidepressant treatment by a psychiatrist (compared to other physicians) was associated with higher odds of being continuously on antidepressant treatment.

Regarding baseline comorbidities, having cancer or renal disease was associated with sustained treatment-free status rather than being continuously on antidepressant treatment. Certain kinds of PPS (backache, musculoskeletal, or gastrointestinal pain) were associated with higher odds of having late re-contacts. The presence of comorbid mental illnesses was associated with higher odds of being on continuous treatment, with the only exception being dementia which was associated with higher odds of sustained cessation of antidepressant treatment.

Table 6.1. Sociodemographic and clinical characteristics

Characteristics	Sustained treatment-free status (n=43,065)	Continuous treatment (n=71,543)	Late re-contact (n=11,863)
Age groups [n (%)]**			
>=85	491 (1.1)	528 (0.7)	74 (0.6)
75-84	3034 (7.0)	5290 (7.4)	679 (5.7)
65-74	4732 (11.0)	10337 (14.4)	1387 (11.7)
55-64	4921 (11.4)	10514 (14.7)	1556 (13.1)
45-54	7916 (18.4)	15956 (22.3)	2401 (20.2)
35-44	8683 (20.2)	15803 (22.1)	2630 (22.2)
25-34	7839 (18.2)	9288 (13.0)	2020 (17.0)
18-24	5449 (12.7)	3827 (5.3)	1116 (9.4)
Sex [n (%)]**			
Male	17129 (39.8)	28326 (39.6)	4316 (36.4)
Female	25936 (60.2)	43217 (60.4)	7547 (63.6)
Depression diagnosis at index visit [n (%)]**			
Major depression	15321 (35.6)	30682 (42.9)	4524 (38.1)
Other depression	27744 (64.4)	40861 (57.1)	7339 (61.9)
Past treatment history [n (%)]**			
Newly diagnosed depression	20448 (47.5)	13273 (18.6)	4161 (35.1)
Non-newly diagnosed depression with history of both AD treatment and depression diagnosis	3454 (8.0)	10953 (15.3)	1224 (10.3)
Non-newly diagnosed depression with history of either AD treatment or depression diagnosis	19163 (44.5)	47317 (66.1)	6478 (54.6)
Physician type at index visit [n (%)]**			
Non-psychiatrist	9407 (21.8)	12319 (17.2)	2264 (19.1)
Psychiatrist	33658 (78.2)	59224 (82.8)	9599 (80.9)
Clinical setting at index visit [n (%)]**			
Outpatient	41317 (95.9)	69339 (96.9)	11483 (96.8)
Emergency service	220 (0.5)	221 (0.3)	51 (0.4)

Inpatient	1528 (3.5)	1983 (2.8)	329 (2.8)
Index AD treatment [n (%)][**]			
SNRI	3899 (9.1)	6465 (9.0)	1027 (8.7)
Other newer AD	1538 (3.6)	2308 (3.2)	365 (3.1)
TCA	3411 (7.9)	6729 (9.4)	1031 (8.7)
Other older AD	7708 (17.9)	13919 (19.5)	2091 (17.6)
Flupentixol/melitracen	2233 (5.2)	2716 (3.8)	601 (5.1)
Use of multiple ADs	3971 (9.2)	9573 (13.4)	1175 (9.9)
SSRI	20305 (47.1)	29833 (41.7)	5573 (47.0)
Baseline physical illnesses [n (%)]			
Chronic obstructive pulmonary disease[**]	6556 (15.2)	11860 (16.6)	1897 (16.0)
Diabetes mellitus[**]	4805 (11.2)	9239 (12.9)	1348 (11.4)
Renal disease	2535 (5.9)	4242 (5.9)	664 (5.6)
Cancer	1924 (4.5)	3148 (4.4)	506 (4.3)
Cardiovascular disease[**]	11790 (27.4)	22368 (31.3)	3409 (28.7)
Baseline painful physical symptoms [n (%)]			
Headache/migraine/dizziness[**]	17158 (39.8)	31074 (43.4)	5187 (43.7)
Back[**]	13489 (31.3)	23998 (33.5)	4191 (35.3)
Musculoskeletal[**]	19645 (45.6)	33812 (47.3)	5721 (48.2)
Gastrointestinal[**]	21979 (51.0)	38031 (53.2)	6448 (54.4)
Others[**]	3337 (7.7)	6071 (8.5)	1038 (8.7)

Baseline mental illnesses [n (%)]			
Schizophrenia**	1535 (3.6)	3991 (5.6)	464 (3.9)
Other psychotic disorders**	900 (2.1)	2148 (3.0)	265 (2.2)
Substance related**	1080 (2.5)	2631 (3.7)	376 (3.2)
Alcohol related**	337 (0.8)	745 (1.0)	117 (1.0)
Drugs related	231 (0.5)	429 (0.6)	61 (0.5)
Bipolar spectrum disorder**	653 (1.5)	2065 (2.9)	231 (1.9)
Dementia**	1751 (4.1)	3189 (4.5)	354 (3.0)
Generalised anxiety disorder**	2085 (4.8)	4873 (6.8)	698 (5.9)
Obsessive-compulsive disorder**	589 (1.4)	1914 (2.7)	273 (2.3)
Panic disorder**	1057 (2.5)	3607 (5.0)	463 (3.9)
Phobic disorder**	274 (0.6)	826 (1.2)	97 (0.8)
Post-traumatic stress disorder**	68 (0.2)	205 (0.3)	22 (0.2)
Sleep disorder**	10011 (23.2)	20045 (28.0)	3249 (27.4)
Attention deficit hyperactivity disorder	26 (0.1)	48 (0.1)	5 (0.0)

Chi-squared test was used (for comparisons between groups by initial outcome statuses); all comparisons were statistically significant with the exceptions being renal disease, cancer, drug-related mental disorder, and attention deficit hyperactivity disorder (not significantly different between groups).
Baseline characteristics were measured over the 12-month pre-index period.
AD=antidepressant; SNRI=serotonin norepinephrine reuptake inhibitor; TCA=tricyclic antidepressant; SSRI=selective serotonin reuptake inhibitor; other newer AD: bupropion and mirtazapine; other older AD: maprotiline, moclobemide, and trazodone.** $p<0.001$

Table 6.2. Service use and costs over the 3-year period[**]

		Sustained treatment-free status (n=43,065)		Continuous treatment (n=71,543)		Late re-contact (n=11,863)	
Service use		% using	mean (SD)[§]	% using	mean (SD)[§]	% using	Mean (SD)[§]
(1st year)	Psychiatric out-patient	84.6	6.63 (6.27)	89.2	12.79 (8.52)	87.5	7.43 (6.71)
	Psychiatric in-patient	5.9	0.09 (0.43)	7.3	0.13 (0.60)	6.0	0.10 (0.46)
	Psychiatric emergency	2.2	0.04 (0.50)	2.2	0.04 (0.47)	2.1	0.04 (0.72)
	Non-psychiatric out-patient	98.0	26.42 (24.10)	98.2	30.46 (28.16)	98.6	30.56 (27.55)
	Non-psychiatric in-patient	21.3	0.42 (1.15)	18.3	0.32 (0.95)	19.7	0.35 (0.98)
	Non-psychiatric emergency	35.2	0.79 (2.53)	33.6	0.88 (4.37)	35.5	0.85 (2.33)
(2nd year)	Psychiatric out-patient	27.1	2.00 (5.06)	85.4	10.37 (8.56)	78.4	6.60 (7.55)
	Psychiatric in-patient	1.5	0.02 (0.23)	5.0	0.09 (0.51)	4.9	0.08 (0.42)
	Psychiatric emergency	0.7	0.01 (0.33)	1.6	0.03 (0.53)	1.6	0.03 (0.45)
	Non-psychiatric out-patient	90.3	24.26 (24.62)	97.8	31.60 (29.28)	98.3	32.02 (28.83)
	Non-psychiatric in-patient	14.2	0.24 (0.81)	18.7	0.33 (0.96)	19.2	0.35 (1.00)
	Non-psychiatric emergency	25.6	0.49 (1.38)	33.5	0.87 (4.00)	35.4	0.89 (2.72)
(3rd year)	Psychiatric out-patient	28.2	2.33 (5.46)	76.4	9.13 (8.89)	59.6	5.32 (7.28)
	Psychiatric in-patient	1.7	0.03 (0.24)	4.6	0.08 (0.46)	3.4	0.06 (0.37)
	Psychiatric emergency	0.7	0.02 (0.33)	1.5	0.03 (0.42)	1.4	0.03 (0.37)
	Non-psychiatric out-patient	88.0	22.70 (23.42)	95.3	30.14 (28.15)	95.7	29.07 (26.95)
	Non-psychiatric in-patient	12.8	0.22 (0.80)	17.4	0.30 (0.92)	16.3	0.29 (0.92)
	Non-psychiatric emergency	23.6	0.46 (1.50)	31.3	0.79 (3.23)	30.4	0.72 (2.67)
Healthcare costs				mean (SD)			
(1st year)	Psychiatric out-patient		465 (554)		1139 (948)		525 (569)
	Psychiatric in-patient		255 (1588)		365 (1956)		290 (1812)
	Psychiatric emergency		2 (17)		2 (20)		2 (21)
	Non-psychiatric out-patient		1236 (2492)		1469 (4440)		1332 (2456)
	Non-psychiatric in-patient		1236 (6086)		526 (2403)		590 (2747)
	Non-psychiatric emergency		88 (259)		80 (364)		80 (241)

	Total	3282 (7143)	3582 (5886)	2818 (4585)
(2nd year)	Psychiatric out-patient	127 (424)	940 (953)	494 (684)
	Psychiatric in-patient	95 (1103)	288 (1822)	257 (1761)
	Psychiatric emergency	1 (12)	2 (25)	2 (22)
	Non-psychiatric out-patient	1041 (2396)	1481 (4861)	1374 (2433)
	Non-psychiatric in-patient	652 (4090)	791.01 (4417)	824 (5106)
	Non-psychiatric emergency	50 (191)	84 (278)	85 (245)
	Total	1966 (5176)	3586 (7328)	3035 (6278)
(3rd year)	Psychiatric out-patient	172 (518)	862 (1046)	453 (780)
	Psychiatric in-patient	111 (1227)	292 (1944)	216 (1722)
	Psychiatric emergency	1 (15)	2 (27)	2 (23)
	Non-psychiatric out-patient	1052 (2525)	1471 (2843)	1345 (2705)
	Non-psychiatric in-patient	614 (4085	824 (4566)	688 (3428)
	Non-psychiatric emergency	53 (199)	88 (293)	81 (290)
	Total	2003 (5306)	3539 (6159)	2785 (5143)

** Chi-squared test was used for categorical variables and ANOVA for continuous variables: all comparisons between groups by initial outcome statuses were statistically significant at a $p<0.001$ with the exceptions being % using, mean number of use, and costs for the 1st year psychiatric emergency services.

§ Number of contacts

Healthcare costs were expressed in international dollars: the 1st year in 2003-2004 international dollars; the 2nd year in 2004-2005 international dollars; the 3rd year in 2005-2006 international dollars.

Table 6.3. Multinomial logistic analysis for sustained treatment-free status and late re-contact (vs. continuous treatment)

	OR (99% CI)	
	Sustained treatment-free status	Late re-contact
Age groups (vs. 18-24)		
>=85	0.601 (0.500, 0.723)**	0.458 (0.325, 0.644)**
75-84	0.402 (0.367, 0.441)**	0.423 (0.365, 0.492)**
65-74	0.337 (0.311, 0.365)**	0.440 (0.388, 0.499)**
55-64	0.354 (0.327, 0.382)**	0.490 (0.435, 0.552)**
45-54	0.381 (0.355, 0.408)**	0.508 (0.456, 0.566)**
35-44	0.428 (0.400, 0.459)**	0.576 (0.518, 0.640)**
25-34	0.634 (0.591, 0.681)**	0.750 (0.672, 0.837)**
Sex: Male vs. Female	1.014 (0.979, 1.050)	0.897 (0.849, 0.948)**
Depression type: Major depression vs. Other depression	0.809 (0.781, 0.839)**	0.870 (0.823, 0.919)**
Past treatment history§		
Newly diagnosed depression	3.336 (3.212, 3.465)**	2.114 (1.992, 2.243)**
Non-newly diagnosed depression with history of both AD treatment and depression diagnosis	0.794 (0.750, 0.840)**	0.833 (0.764, 0.909)**
Physician type: Non-psychiatrist vs. Psychiatrist	1.448 (1.383, 1.515)**	1.199 (1.116, 1.289)**
Clinical setting (vs. In-patient)		
Out-patient	0.889 (0.806, 0.981)*	1.023 (0.871, 1.203)
Emergency service	0.969 (0.732, 1.282)	1.099 (0.712, 1.697)
Index AD treatment (vs. SSRI)		
SNRI	0.906 (0.853, 0.963)**	0.854 (0.777, 0.940)**
Other newer AD	0.947 (0.862, 1.040)	0.815 (0.700, 0.948)**
TCA	0.851 (0.799, 0.907)**	0.885 (0.804, 0.975)*
Other older AD	0.889 (0.848, 0.932)**	0.854 (0.793, 0.919)**
Flupentixol/melitracen	1.271 (1.170, 1.381)**	1.208 (1.065, 1.369)**
Use of multiple ADs	0.649 (0.612, 0.687)**	0.671 (0.614, 0.733)**
Presence of baseline physical illnesses		
Chronic obstructive pulmonary disease	1.009 (0.962, 1.058)	1.043 (0.969, 1.122)
Diabetes mellitus	1.035 (0.980, 1.093)	1.002 (0.919, 1.091)
Renal disease	1.170 (1.088, 1.259)**	1.055 (0.940, 1.184)

Cancer	1.232 (1.136, 1.336)**	1.106 (0.972, 1.258)
Cardiovascular disease	0.990 (0.949, 1.033)	1.012 (0.948, 1.080)
Presence of baseline painful physical symptoms		
Headache/migraine/dizziness	0.973 (0.939, 1.010)	1.030 (0.974, 1.089)
Back	1.000 (0.962, 1.040)	1.116 (1.052, 1.184)**
Musculoskeletal	1.040 (1.003, 1.078)*	1.063 (1.005, 1.125)*
Gastrointestinal	1.022 (0.986, 1.058)	1.068 (1.011, 1.128)*
Others	1.025 (0.962, 1.091)	1.053 (0.959, 1.157)
Presence of baseline mental illnesses		
Schizophrenia	0.719 (0.660, 0.783)**	0.744 (0.651, 0.850)**
Other psychotic disorders	0.917 (0.822, 1.023)	0.885 (0.744, 1.052)
Substance related	0.874 (0.786, 0.972)*	1.003 (0.857, 1.175)
Alcohol related	1.153 (0.956, 1.390)	1.270 (0.963, 1.674)
Drugs related	1.107 (0.884, 1.387)	0.978 (0.682, 1.403)
Bipolar spectrum disorder	0.784 (0.694, 0.887)**	0.843 (0.701, 1.013)
Dementia	1.166 (1.069, 1.272)**	0.864 (0.740, 1.008)
Generalised anxiety disorder	0.904 (0.840, 0.973)**	0.938 (0.840, 1.046)
Obsessive-compulsive disorder	0.688 (0.606, 0.781)**	0.998 (0.841, 1.186)
Panic disorder	0.689 (0.626, 0.758)**	0.881 (0.771, 1.006)
Phobic disorder	0.741 (0.615, 0.893)**	0.784 (0.592, 1.038)
Post-traumatic stress disorder	0.891 (0.614, 1.291)	0.787 (0.440, 1.409)
Sleep disorder	0.918 (0.882, 0.955)**	1.038 (0.977, 1.102)
Attention deficit hyperactivity disorder	0.884 (0.461, 1.696)	0.594 (0.176, 2.007)

OR=odds ratio; CI=confidence interval; AD=antidepressant; SNRI=serotonin norepinephrine reuptake inhibitor; TCA=tricyclic antidepressant; SSRI=selective serotonin reuptake inhibitor; other newer agents: bupropion and mirtazapine; other older agents: maprotiline, moclobemide, and trazodone.
**p<0.001;*p<0.01; §Reference group=non-newly diagnosed depression with history of either AD treatment or depression diagnosis.

Table 6.4. Multivariable analysis of total healthcare costs for the consecutive 3 years

	RR (99% CI)		
	1st year costs	2nd year costs	3rd year costs
Outcome status (vs. late re-contact)			
Sustained treatment-free status	1.051 (1.030, 1.072)**	0.668 (0.652, 0.684)**	0.777 (0.757, 0.798)**
Continuous treatment	1.222 (1.199, 1.246)**	1.087 (1.062, 1.112)**	1.176 (1.147, 1.206)**
Age groups (vs. 18-24)			
>=85	1.723 (1.619, 1.834)**	2.737 (2.518, 2.975)**	2.964 (2.694, 3.261)**
75-84	1.469 (1.426, 1.514)**	2.278 (2.194, 2.365)**	2.409 (2.312, 2.509)**
65-74	1.250 (1.218, 1.283)**	1.892 (1.832, 1.955)**	2.027 (1.957, 2.099)**
55-64	1.080 (1.053, 1.108)**	1.577 (1.528, 1.626)**	1.699 (1.643, 1.757)**
45-54	0.968 (0.946, 0.990)**	1.339 (1.302, 1.378)**	1.405 (1.363, 1.448)**
35-44	0.935 (0.915, 0.957)**	1.235 (1.202, 1.270)**	1.295 (1.257, 1.334)**
25-34	0.932 (0.910, 0.954)**	1.191 (1.157, 1.226)**	1.226 (1.188, 1.265)**
Sex: Male vs. Female	1.090 (1.077, 1.102)**	1.046 (1.031, 1.060)**	1.067 (1.051, 1.083)**
Depression type: Major depression vs. Other depression	1.079 (1.067, 1.092)**	1.065 (1.050, 1.080)**	1.074 (1.058, 1.091)**
Past treatment history §			
Newly diagnosed depression	1.045 (1.031, 1.058)**	0.980 (0.965, 0.996)*	0.982 (0.966, 1.000)*
Non-newly diagnosed depression with history of both AD treatment and depression diagnosis	1.079 (1.061, 1.098)**	1.061 (1.038, 1.084)**	1.061 (1.036, 1.086)**
Physician type: Non-psychiatrist vs. Psychiatrist	1.035 (1.020, 1.051)**	1.029 (1.010, 1.049)**	1.028 (1.008, 1.049)**
Clinical setting (vs. In-patient)			
Out-patient	0.450 (0.436, 0.465)**	0.671 (0.644, 0.699)**	0.684 (0.654, 0.716)**
Emergency service	0.672 (0.613, 0.737)**	0.816 (0.728, 0.915)**	0.779 (0.688, 0.881)**
Index AD treatment (vs. SSRI)			
SNRI	1.176 (1.153, 1.199)**	1.079 (1.053, 1.105)**	1.069 (1.041, 1.097)**
Other newer AD	1.119 (1.085, 1.154)**	1.076 (1.036, 1.118)**	1.024 (0.983, 1.067)
TCA	0.906 (0.888, 0.924)**	1.011 (0.986, 1.037)	0.982 (0.956, 1.009)
Other older AD	0.950 (0.936, 0.965)**	1.003 (0.984, 1.022)	1.020 (0.999, 1.041)
Flupentixol/melitracen	0.880 (0.856, 0.905)**	1.007 (0.973, 1.041)	0.978 (0.943, 1.014)
Use of multiple ADs	1.120 (1.100, 1.140)**	1.089 (1.065, 1.113)**	1.082 (1.056, 1.108)**

Presence of baseline physical illnesses			
Chronic obstructive pulmonary disease	1.093 (1.076, 1.109)**	1.089 (1.069, 1.110)**	1.131 (1.108, 1.154)**
Diabetes mellitus	1.220 (1.199, 1.242)**	1.278 (1.250, 1.306)**	1.288 (1.258, 1.319)**
Renal disease	1.178 (1.150, 1.207)**	1.235 (1.198, 1.273)**	1.251 (1.210, 1.293)**
Cancer	1.291 (1.257, 1.326)**	1.214 (1.173, 1.257)**	1.259 (1.212, 1.307)**
Cardiovascular disease	1.128 (1.113, 1.143)**	1.117 (1.099, 1.136)**	1.068 (1.049, 1.087)**
Presence of baseline painful physical symptoms			
Headache/migraine/dizziness	1.028 (1.016, 1.040)**	1.031 (1.016, 1.045)**	1.049 (1.032, 1.065)**
Back	1.056 (1.043, 1.069)**	1.029 (1.013, 1.045)**	1.037 (1.020, 1.054)**
Musculoskeletal	1.060 (1.048, 1.073)**	1.076 (1.061, 1.092)**	1.074 (1.058, 1.091)**
Gastrointestinal	1.048 (1.036, 1.060)**	1.029 (1.015, 1.044)**	1.039 (1.024, 1.055)**
Others	1.078 (1.056, 1.099)**	1.049 (1.024, 1.076)**	1.061 (1.033, 1.090)**
Presence of baseline mental illnesses			
Schizophrenia	1.571 (1.530, 1.613)**	1.745 (1.689, 1.803)**	1.785 (1.723, 1.848)**
Other psychotic disorders	1.074 (1.038, 1.111)**	1.068 (1.024, 1.114)**	1.155 (1.104, 1.209)**
Substance related	1.224 (1.184, 1.265)**	1.287 (1.235, 1.341)**	1.328 (1.270, 1.388)**
Alcohol related	1.369 (1.291, 1.452)**	1.469 (1.364, 1.582)**	1.553 (1.431, 1.686)**
Drugs related	1.088 (1.012, 1.170)**	1.033 (0.943, 1.131)	1.070 (0.969, 1.182)
Bipolar spectrum disorder	1.151 (1.111, 1.194)**	1.176 (1.124, 1.230)**	1.177 (1.122, 1.235)**
Dementia	1.199 (1.166, 1.234)**	1.226 (1.183, 1.271)**	1.257 (1.208, 1.308)**
Generalised anxiety disorder	0.983 (0.961, 1.005)	0.957 (0.930, 0.984)**	0.966 (0.937, 0.995)*
Obsessive-compulsive disorder	1.031 (0.993, 1.070)	1.034 (0.988, 1.082)	1.084 (1.032, 1.138)**
Panic disorder	0.923 (0.898, 0.949)**	0.910 (0.880, 0.942)**	0.957 (0.923, 0.993)*
Phobic disorder	0.943 (0.892, 0.997)*	0.974 (0.910, 1.044)	0.936 (0.870, 1.008)
Post-traumatic stress disorder	1.067 (0.954, 1.193)	1.157 (1.009, 1.326)*	1.295 (1.119, 1.499)**
Sleep disorder	1.029 (1.016, 1.042)**	1.047 (1.030, 1.063)**	1.042 (1.025, 1.060)**
Attention deficit hyperactivity disorder	0.890 (0.717, 1.104)	0.978 (0.750, 1.275)	1.024 (0.771, 1.361)
Baseline total healthcare expenditures (in 1000 international dollars)	1.159 (1.155, 1.162)**	1.161 (1.156, 1.166)**	1.157 (1.151, 1.162)**

RR=relative risk; CI=confidence interval; AD=antidepressant; SNRI=serotonin norepinephrine reuptake inhibitor; TCA=tricyclic antidepressant; SSRI=selective serotonin reuptake inhibitor; other newer AD: bupropion and mirtazapine; other older AD: maprotiline, moclobemide, and trazodone.
**p<0.001; *p<0.01; §Reference group=non-newly diagnosed depression with history of either AD treatment or depression diagnosis.

Factors associated with total costs in the years after initial treatment

The analysis of total healthcare costs over the subsequent three years (Table 6.4) revealed that sustained treatment-free status was associated with the lowest total costs in the second and third years compared to either patients who were on continuous treatment or those who had late re-contacts.

Beyond the first year, total costs appeared to increase consistently with age, and this trend became more prominent through the second year to third year. Male gender was associated with higher total costs for all three years, as was having a diagnosis of MDD. In these models, patients who were diagnosed by non-psychiatrists on the index date had higher total costs for the subsequent three years as did those diagnosed when they were inpatients. The presence of physical comorbidities and PPS were associated with higher costs for all three years. Having comorbid mental illnesses was generally associated with higher total costs, with exceptions being generalised anxiety disorder (GAD), panic disorder, and phobic disorder which were associated with lower costs.

6.4. Discussion

This chapter has described the distributions of treatment outcomes after initial antidepressant treatment in a real-world setting using data from a large national cohort. Demographic and clinical factors associated with treatment outcomes were also explored. These analyses have added to the evidence base by showing that treatment outcomes following initial antidepressant treatments can impact total healthcare costs

over the longer-term. Specifically, patients who experienced sustained treatment-free status following initial treatment were found to have significantly lower costs in the second and third years after the index date, compared to those with less favourable outcomes. In addition, treatment outcomes and total costs differed according to initial choice of antidepressants as well as the presence of comorbid mental disorders and PPS.

The impact of treatment outcome status on costs

The focus in this chapter on *sustained* treatment-free status is relevant in assessing the impacts of treatment outcomes over a longer-term follow-up since a high relapse/recurrence rate has previously been reported within the first six to twelve months of follow-up (Lin et al., 1998; Paykel, 1998; Shapiro and Keller, 1981). Although elsewhere a high rate of recovery (67.5%) has been reported during the first six months following treatment (Bottomley et al., 2010), earlier studies showed that only 30% of recovered patients remain in recovery and symptom-free during a one-year follow-up (Keller and Shapiro, 1981). This is in accordance with the current results that around 34% of subjects were classified as having sustained treatment-free status over the 18-month period of observation. In addition, the time course following discontinuation of treatment has been shown to be an important factor in determining the probability of relapse or recurrence. The risk of relapse is greatest shortly after recovery, especially in the first three to six months, and decreases over time (Keller, 2003; Solomon et al., 2000). Therefore, to assess the real impact of treatment outcomes, it is important to evaluate the effect of sustained treatment-free status while taking into account re-contacts soon after this.

In this chapter, patients who achieved sustained treatment-free status after initial treatment have lower total costs in the second and third years after the index date compared to those with less favourable outcomes. The evidence from similar previous studies has been limited to examining service use and costs in the first six or twelve months following initial treatment, and these may include the treatment that led to the treatment outcomes. In this chapter, it was found that first year costs were higher for those patients achieving sustained treatment-free status than those who experienced late re-contacts. Compared to service use and costs for those who achieved sustained treatment-free status in the first year, it is noteworthy that their use of psychiatric or non-psychiatric services clearly decreased in the second and third years. An interpretation of this result could be that the higher total first year costs for those who achieved sustained treatment-free status may be due to the treatment required to achieve the sustained treatment-free status which then reduces costs in subsequent years. However, patients with insufficient treatment in the first year may then have higher costs subsequently as a result of not experiencing sustained treatment-free status.

Depression type, physician specialty, and other clinical characteristics

Patients with a diagnosis of MDD were more likely to remain on treatment than to be in either sustained treatment-free status or to have late re-contacts. A diagnosis of MDD at the index visit also predicted higher costs in the subsequent three years. In contrast, newly diagnosed depression was associated with sustained treatment-free status rather than being on continuous treatment, compared to those patients who had been diagnosed or treated prior to the index date. Having newly diagnosed depression

was also associated with lower costs in the second and third years. Regarding treatment setting on the index date, patients who had been diagnosed by a psychiatrist were more likely to be on continuous treatment, and they were found to have lower total costs over the three-year follow-up period than those diagnosed by a non-psychiatrist. Patients who were initially diagnosed in inpatient settings were more likely to subsequently have sustained treatment-free status rather than being on continuous treatment despite the fact that this was associated with higher total costs for the following years.

These results support those from a previous study (Sobocki et al., 2006) in finding that disease severity could be an important factor in determining treatment outcomes after initial treatment. Although speculative, being diagnosed in inpatient settings could imply that depression is diagnosed through a psychiatric consultation during hospitalisation with it not being the primary disease leading to the hospitalisation. Conversely, a diagnosis of MDD, being diagnosed from a psychiatrist, or the presence of a prior history of treatment/or a diagnosis, could be indicators of greater disease severity and thus poorer outcome. Patients with non-newly diagnosed depression were shown to be least likely to have sustained treatment-free status as well as to have the highest costs in each of the three follow-up years, which may be related to the more chronic disease course. Along with increased age and physical comorbidities (discussed below), patients initially diagnosed in inpatient settings or diagnosed by a non-psychiatrist, possibly implying the presence of medical conditions, had higher total healthcare costs for each of the three years during the follow-up.

Choice of initial antidepressants

People prescribed with selective serotonin reuptake inhibitors (SSRIs) were more likely to have sustained treatment-free status than being on continuous treatment compared to patients prescribed other antidepressants (except flupentixol/melitracen); they were also more likely to have late re-contacts (Table 6.3). Flupentixol/melitracen was shown to be different from other antidepressants in having higher odds of sustained treatment-free status than SSRIs. To put this into context, 84.1% of the patients initially prescribed with flupentixol/melitracen were cases with depression other than MDD. Patients prescribed with SSRIs, compared to the overall sample, were also younger and more likely to be newly diagnosed with depression (also see Table 4.2). As patients with these characteristics tended to have an outcome profile of either sustained treatment-free status or late re-contacts, it seems probable that treatment outcomes for patients prescribed SSRIs may be partly accounted for by such characteristics.

Compared to patients prescribed SSRIs, those prescribed serotonin norepinephrine reuptake inhibitors (SNRIs) and multiple antidepressants at the index visit had higher total costs over the subsequent three years. One interpretation is that patients with initial presentations of greater disease severity were more likely to be prescribed with SNRIs or multiple antidepressants than SSRIs, thus generating higher costs. Meanwhile, those prescribed tricyclic antidepressants (TCAs) or other older antidepressants had costs that did not differ significantly in the second and third years despite their lower total costs in the first year. This is consistent with a previous systematic review showing that while higher non-depression-related costs and lower

depression-related costs were found in TCA users in some studies, patients using TCAs generally had comparable healthcare costs to those using SSRIs in database studies (Pan et al., 2012). As comparable efficacy has been often reported between SSRIs and TCAs, what the current findings may add to the evidence base is that by showing that after taking into account treatment outcomes, total healthcare costs do not differ between patients prescribed SSRIs and older generation antidepressants over a longer-term follow-up.

Physical comorbidities and painful physical symptoms

Contrary to the presence of physical comorbidities and PPS being associated with higher total costs in each of the three follow-up years, these baseline comorbidities were shown to have different impacts on treatment outcomes. The presence of cancer or renal disease was associated with higher odds of having sustained treatment-free status than being on continuous treatment, while the presence of certain types of PPS was related to higher odds of having late re-contacts. Previous studies have conceptualised a variety of reasons for the occurrence of depressive disorders in patients with physical illnesses, including depression being a secondary psychological reaction (Katon, 2003). Therefore, the current results might be interpreted as depression in patients with cancer or renal disease being a psychological reaction, and thus potentially transient. Patients with these physical illnesses may also tend to stop antidepressants quickly after depressive symptoms improve as the perceived side-effects can be particularly intolerable with a major physical illness. This phenomenon could furthermore indicate that depression may be under-recognised or under-treated in those with serious physical health problems.

Pain and depression are among the top causes of quality-adjusted life-year (QALY) losses in primary care (Fernandez et al., 2010) and co-occurring pain complaints are commonly prevalent in depressed patients (Bair et al., 2003; Husain et al., 2007; Ohayon and Schatzberg, 2003). Patients with PPS have been shown to be less likely to achieve remission following acute treatment for depression (Fava et al., 2004), and the current analysis concurs with these previous studies in finding that having certain PPS (backache, musculoskeletal, and GI pain) is associated with late re-contacts. Higher healthcare utilisation and costs have also been found in depression with PPS in other studies (Gameroff and Olfson, 2006). The current findings add to this evidence base by showing that the presence of each kind of PPS at baseline is associated with an increase in total healthcare costs, not only in the first year but also in the second and third years.

Comorbid mental disorders

In the current analysis, the presence of most comorbid mental disorders was associated with decreased odds of sustained treatment-free status and increased odds of staying on continuous treatment, with the only exception being dementia. Despite the existence of conflicting findings from studies with relatively short follow-up periods (Ryu et al., 2005), depressive symptoms in dementia have been shown rarely to persist over a longer-term follow-up, e.g. two years (Aalten et al., 2005; Savva et al., 2009; Wetzels et al., 2010). Over time, depression has tended to decrease while apathy has increased in these patients (Aalten et al., 2005; Wetzels et al., 2010). Another study also found a high resolution rate of depressive symptoms for patients with dementia (Bergh et al., 2011). In addition, there has been evidence supporting

depression as a prodrome of dementia (Amieva et al., 2008; Wilson et al., 2010). Therefore, one possible interpretation of the results could be that depression occurs over certain stages in the course of dementia and disappears later when the illness progresses.

The presence of comorbid mental disorders was associated with increased costs in the following years with the exceptions of GAD, panic, and phobic disorder. Patients with anxiety disorders have been shown to be less likely to use services compared to those with mood disorders (Alonso et al., 2004b; Mojtabai et al., 2002); they have also been shown to have reduced *perceived* need for help (Mojtabai et al., 2002). It seems probable that the lower service use and costs of these patients may be largely influenced by the nature of their anxiety disorders, especially in their use of mental health services and this could be particularly the case when the anxiety problems dominate patients' clinical presentations. However, the extent to which these anxiety-related problems of patients can influence their health behaviours regarding physical conditions remains to be determined.

6.5. Implications and limitations

Implications and policy recommendations

The choice of index antidepressants between SSRIs and older generation antidepressants did not reveal significant differences in healthcare costs in the second and third years following the start of the treatment episode while prescriptions of multiple antidepressants at the index visit, although possibly influenced by physician

preferences and the nature of the depressive disorders, was associated with higher total healthcare costs in the following years, implying that initial prescription of a single antidepressant may be preferable in order to constrain costs.

Patients not achieving sustained treatment-free status were shown to have higher healthcare costs in the follow-up years. As shown elsewhere (Pan et al., 2013c), patients remaining engaged with antidepressant treatment within the first three months after the index visit have higher odds of achieving sustained treatment-free status and lower odds of having late re-contacts over the 18-month period. Endeavours to reduce early attrition - probably through shared decision-making and proper patient-physician communication - to improve initial treatment outcome of depression could be emphasised to reduce total healthcare costs in the subsequent years.

Limitations and conclusions

As service use data contained in the NHIRD includes only health services provided by the NHI system in Taiwan, the perspective of the current analysis was relatively limited, and it was not possible to analyse wider economic impacts outside the health system. The lack of information on clinical symptoms and use of a proxy definition is clearly a major limitation. Ending psychopharmacological therapy may be for complex reasons other than achieving good clinical response, e.g. experiences of side-effects of medications. However, with the 18-month observation period in this chapter, the sustained treatment-free status seems likely to indicate initial treatment effectiveness without later clinical fluctuations sufficient to trigger a medical contact when simultaneously specifying another subgroup of subjects who have later

re-contacts which may reflect changes in clinical conditions in which help-seeking is considered beneficial (Pan et al., 2013c).

Moreover, as a secondary analysis of a large healthcare database, the analysis of the patterns of care and related costs over time may require combining further information from other sources such as bottom-up longitudinal studies of treated prevalence, and prior expert knowledge to give firmer conclusions. A replication study with a more recent cohort in Taiwan may be also warranted to reflect changes in the healthcare system over time as well as its associated impacts on subjects' service use and healthcare costs.

Factors which may further limit generalisability of the current findings include differences in the insurance system and the role of private health insurance between countries. As seen in this chapter, most patients with depression received specialised treatment from psychiatrists which is quite different from countries in which a referral system has been emphasised. Within the NHI system in Taiwan, patients can easily have access to specialists without referrals from general practitioners and with affordable co-payments. Therefore, this unique medical environment of Taiwan should be borne in mind while interpreting these results.

In conclusion, this analysis, based on a large national cohort, suggests that the outcome status following initial treatment could exert an impact on total healthcare costs in the second and third years after the index date. Furthermore, the presence of comorbid anxiety disorders and PPS seem to affect healthcare costs over the longer-term. It is important for both physicians and policy-makers to further improve

initial treatment outcomes of depression through effective strategies. Future endeavours to explore the impacts of comorbid anxiety disorders and PPS on health service use and treatment of depression are warranted.

Chapter 7. Cost-effectiveness and cost-utility analyses of antidepressant treatment

The purpose of this chapter is twofold: first to compare the cost-effectiveness and cost-utility of different categories of antidepressant treatments and second to test whether and how the presence of cardiovascular diseases (CVD) affects these results.

7.1. Introduction

In Chapter 4, a cost analysis was presented which explored relationships between demographic and clinical characteristics and healthcare costs for patients with depression. Comorbid CVD and headache were found to be associated with both higher non-psychiatric and psychiatric costs. In Chapter 6, a group of patients out of the whole cohort was further defined (who initially received minimal treatment of three visits within the first three months) and costs for the consecutive three years after the index date were compared between patients in different treatment outcome groups. As seen in previous chapters, various categories of antidepressant treatments were associated with total and psychiatric costs. Whether the categories of antidepressants differ in terms of cost-effectiveness and cost-utility remains to be determined. This is addressed in the current chapter where such analyses are conducted.

As stated in a previous chapter, depression frequently co-occurs with CVD (Joynt et al., 2003).Globally, while depression is among the top-ranking causes of disability (Vos et al., 2012), CVD constitutes the leading cause of premature death (Lozano et

al., 2012). The health and economic burdens of depression and CVD are great individually, but they can be substantially more pronounced when the two conditions co-occur. Indeed, an additive effect of major depressive disorder (MDD) and CVD on health related quality of life has previously been reported (O'Neil et al., 2013).

Although compelling evidence has suggested depression, over physiological factors like left ventricular ejection fraction and ischemia, as having the most important influence on health related quality of life of cardiac patients (Ruo et al., 2003), it is less clear how the relationship between depression and health related quality of life is attenuated by the presence of CVD. While treating one condition could subsequently impact the other pre-existing condition, resulting in lower quality of life than would be expected as a result of the pre-existing condition on its own, the extent to which comorbid CVD may impact patients' quality of life during the course of depression treatment remains unclear. Given the huge burdens of these conditions as well as CVD being the most prevalent comorbid physical condition (26.9%) considered in this study (see Table 4.1), it is important that the economic impact of depression treatment on quality of life be examined in the presence of comorbid CVD.

There are certain issues regarding existing evidence. First, most previous studies comparing the cost per quality-adjusted life-year (QALY) between antidepressant treatments have been modelling exercises (Pirraglia et al., 2004). These are useful and an be adaptped to different situations, but they are based on a variety of assumptions (Haji Ali Afzali et al., 2012). Only a limited number of prospective studies addressing the cost-utility of antidepressant treatments have been conducted (Kendrick et al., 2006; Serrano-Blanco et al., 2009) and sample sizes have been small and may not be

representative. Third, the findings from those prospective studies are conflicting (Kendrick et al., 2006; Serrano-Blanco et al., 2009). One study suggested that selective serotonin reuptake inhibitors (SSRIs) are more cost-effective than tricyclic antidepressants (TCAs) (Kendrick et al., 2006) but findings from the other study suggested treatment with a TCA dominated fluoxetine (a SSRI) (Serrano-Blanco et al., 2009). Fourth, the impact of major comorbidities like CVD on costs and QALYs for individual antidepressant treatments remains unknown. Finally, most of the existing data are from Western countries. Whether individual antidepressant treatments are cost-effective in terms of improving quality of life in Asian countries like Taiwan needs to be determined.

The aim of this chapter is to compare the cost-effectiveness and cost-utility between individual antidepressants from the healthcare perspective. To further address the effects of comorbid CVD, the analyses are conducted taking into account the presence or not of this condition.

7.2. Methods

Data

As in earlier chapters, data were extracted from the National Health Insurance Research Database (NHIRD) in Taiwan. In this chapter, subjects were first identified from the NHIRD according to inclusion criteria (see below) and the index date was defined as the date on which the subject was first prescribed an antidepressant for treatment of depressive disorders in 2003. A two and half year dataset containing all

NHI healthcare information on each subject spanning the index date (one year preceding, and one and half years following) was then established.

Participants

In contrast to earlier chapters, a narrower inclusion criterion was used. Specifically, only patients who were initially prescribed SSRIs, SNRIs or TCAs, were included. Therefore, patients receiving other newer antidepressants (bupropion and mirtazapine), other older antidepressants (maprotiline, moclobemide, and trazodone), flupentixol/melitracen and multiple antidepressants at the index date were excluded.

In summary, participants aged 18 or over meeting the following criteria were included:

- At least one prescription for an antidepressant of interest (SSRIs, SNRIs and TCAs) for treatment of MDD or other depression in 2003.
- Data available for a minimum of 12 months before the index date and 18 months after the index date.
- At least three antidepressant prescriptions in the first three months after the index date or at least four prescriptions over the 18-month observation period despite having had less than three antidepressant prescriptions in the first three months after the index date.

Definition of treatment outcome status

As discussed in Chapter 5, a proxy criteria for remission – antidepressant cessation for

at least six months (Sicras-Mainar et al., 2010a) – was modified and then employed in this chapter. This database measure of remission has been previously examined for its validity with an acceptable level of concordance with clinical criteria reported (Cronbach's alpha 90.6%, 95% CI 85.6, 95.6) (Sicras-Mainar et al., 2010a). It was further required in this thesis that there were no late re-contacts (defined as a restart of antidepressants) noted during the 18-month observation period to be considered having a 'sustained treatment-free status'. Study participants were therefore divided into three mutually exclusive groups:

- Sustained treatment-free status: patients who had an antidepressant cessation for at least six months and had not restarted antidepressant use by the end of the observation period.
- Continuous treatment: patients who had not had an antidepressant cessation for at least six months.
- Late re-contact: patients who had an antidepressant cessation for at least six months and had restarted antidepressant use after the cessation of antidepressant treatment.

Observation period for treatment outcome

For each individual, the observation period started on the index date and continued for 18 months. The additional six-months after the first 12 months were included to ensure adequate time had elapsed to assess whether treatment-free status had been achieved. The treatment-free period, i.e. cessation of antidepressant treatment, could begin at any point during the 12 months after the index date (see Figure 6.1), but a

participant needed to have remained off antidepressants for a minimum of six months to fulfill the definition. Hence, a maximum observation period of 18 months for attaining treatment outcome was needed.

Utility weights

The baseline utility scores were from a naturalistic longitudinal observational study with 447 patients recruited at 56 Swedish primary care centres (Sobocki et al., 2007). The inclusion criteria of that study were similar to the current analyses (patients older than 18 years who initiated an antidepressant therapy in clinical settings because of depression); the sample size was reasonably large and patient composition was representative (comprising a heterogeneous population of patients with depression ranging from mild to severe cases). The EuroQol five-dimensions (EQ-5D) questionnaire was completed at each visit by the patients and used to generate utility scores. The baseline utility score for patients with MDD in this chapter was set at 0.42 assuming a heterogeneous group of MDD patients comprising those with moderate (79.6%, utility=0.46) and severe (20.4%, utility=0.27) depression as in that study; baseline utility scores for those with other depression was assumed to be 0.60 (Sobocki et al., 2007).

The utility score for the 'sustained treatment-free status' health state was set at 0.85 (equivalent to 'responders remitters' in Sapin et al (2004). It was further assumed that people who remained off antidepressants for six months but resumed them later would have the same utility, 0.72, as those 'responders non-remitters' (Sapin et al., 2004) at the time when they were off antidepressants.

As people who remained on continuous treatment would likely comprise a group of patients with heterogeneous disease severity, a utility score of 0.66 was adopted from those who remained on antidepressants and were followed-up for a mean of 165 days in the naturalistic observational study of Sobocki et al. (2007). The utility score for the 'late re-contact' health state in the current analyses was set at 0.47 – the baseline mean utility score of depressed patients from the same study. The uncertainty in the utility scores of the 'late re-contact' health state and 'continuous treatment' health state (95% confidence interval 0.53, 0.75) as well as other utility values were tested later in the section of sensitivity analyses.

Estimation of quality-adjusted life years

By applying the above utility scores, the QALY profiles over the 12 months after the index date were estimated using area-under-the-curve methods based on the following assumptions:

- Sustained treatment-free status: a linear increase from the baseline utility score (MDD=0.42 and other depression=0.60) to the 'sustained treatment-free status' health state (0.85) over the 12-month period.
- Late re-contact: a linear increase from the baseline utility score (0.42 or 0.60) to the 'responders non-remitters' health state (0.72) over the initial six-month period, followed by a linear deterioration back to the 'late re-contact' health state (0.47) over the remaining six months.
- Continuous treatment: a linear increase from the baseline utility score (0.42 or 0.60) to the 'continuous treatment' health state (0.66) over the 12-month treatment

period.

Demographic and clinical information

Demographic and clinical data, including age, gender, diagnosis of depressive disorders (MDD vs. other depression), initial choice of antidepressants (SSRIs, SNRIs and TCAs), physician specialty, and clinical setting on the index date were extracted. Participants were grouped according to past treatment history, i.e. newly diagnosed depression (those who were free of antidepressant use or a depression diagnosis for a minimum of 12 months before the index date) and non-newly diagnosed depression.

Baseline characteristics regarding comorbid mental disorders, physical illnesses (CVD, diabetes mellitus, chronic obstructive pulmonary disease, renal diseases, and cancer), several kinds of painful physical symptoms, as well as healthcare expenditure were extracted for all subjects for the 12 months prior to the index date.

Economic evaluation

Service use components extracted from the NHIRD included outpatient contacts, emergency attendances, and inpatient stays for all reasons. All costs were calculated from the actual claims data, were described by categories of services, e.g. psychiatric costs, non-psychiatric costs, and total costs, and were expressed in international dollars (the implied PPP conversion rate between 2003-2004 New Taiwan Dollar (NTD) and international dollar is 20.43:1) (World Economic Outlook (WEO) data, 2013). However, the figures in the local national currency, NTD, instead of

international dollars, were used to interpret results along with the willingness-to-pay data in Taiwan expressed in NTD.

A cost-effectiveness and a cost-utility analysis were conducted from the perspective of healthcare providers. Comparative analyses were undertaken between antidepressant treatment groups on both psychiatric and total costs. Rates of sustained treatment-free status (i.e. treatment success) and QALYs accrued during the 12-month period were compared between treatment groups. Incremental cost-effectiveness ratios (ICERs) and incremental cost-utility ratios (ICURs), defined as the difference in costs divided by the difference in outcomes (rates of sustained treatment-free status, QALYs accrued) were calculated.

As stated at the beginning of the chapter, one of the aims is to assess the cost-effectiveness and cost-utility of antidepressant treatments in the context of comorbid CVD. Therefore, these analyses were first performed using the full study sample, then all analyses were compared in subgroups defined by whether participants had comorbid CVD or not. To aid interpretability as well as to address potential selection bias with treatment groups in this real-world sample, the probability that an antidepressant therapy is cost-effective compared with the alternatives as a function of the decision makers' maximum willingness-to-pay for an additional QALY was illustrated by cost-effectiveness acceptability curves (CEACs) (Briggs et al., 1997) while controlling for above mentioned demographic and clinical factors. The methods used for analyses, e.g. for constructing CEACs, were described in Chapter 3.

Statistical analyses

Unadjusted costs and QALYs gained were first compared using ANOVA while rates of sustained treatment-free status were compared via chi-squared tests between treatment groups. Then, adjusted means of costs and QALYs for antidepressant groups were obtained by linear regression analyses in which demographic and clinical covariates (as described in earlier section of demographic and clinical information) were controlled for. Adjusted rates of sustained treatment-free status for treatment groups were obtained by logistic regression while simultaneously taking other covariates into consideration. ICERs (incremental psychiatric cost per percentage point of treatment success) and ICURs (incremental psychiatric cost per QALY gained) were then calculated based on those adjusted estimates.

The robustness of the results was confirmed using nonparametric bootstrapping techniques to account for any non-normality in their distribution. The original dataset was used to generate 1000 resamples and mean differences, P-values and confidence intervals were computed with demographic/clinical covariates being controlled for. CEACs were constructed using the net benefit approach (Briggs, 2001; Briggs et al., 1997). That is, a range of willingness-to-pay values for an additional QALY gained was mapped alongside the proportion of the estimates of the net benefit values above zero for which an antidepressant of interest was more cost-effective over the alternatives. The range of willingness-to-pay values considered were from NTD 0 to 3,000,000 (roughly equal to £0-60,000; international dollars 0-150,000). This approach assumes that there is a theoretical but not necessarily known value that society would place on a gain of one extra QALY. NTD 1,500,000 (equal to £30,000;

international dollars 75,000) and 2,000,000 (equal to £40,000; international dollars 100,000) were considered as 'the threshold values' (Shiroiwa et al., 2010).

Sensitivity analyses

To examine the responsiveness of cost-utility results to changes in different utility weights, sensitivity analyses were also performed. The four scenarios included: (i) varying the utility weights for the 'continuous treatment' health state to the highest value (0.75); (ii) varying the utility weights for the 'continuous treatment' health state to the lowest value (0.53); (iii) varying the utility weights for the 'late re-contact' health state to the baseline value, i.e. 0.42 for those with baseline MDD and 0.60 for those with other depression (assuming the relapses of depression would revert back to baseline severity for each subject); and (iv) varying the utility weights for the 'late re-contact' health state to a lower value (0.27) (assuming the relapse of depression would be of severe severity for each subject).

7.3. Results

Study population

A total of 96,501 adult individuals in the NHIRD met the inclusion criteria for the study. The number with comorbid CVD was 27,484 (12.4% SNRI, 17.1% TCA, 70.4% SSRI) and 69,017 were without CVD (14.5% SNRI, 13.6% TCA, 71.9% SSRI). Patients prescribed TCAs were older than those prescribed SSRIs and SNRIs (Table 7.1; also see Table 4.2). There were more cases of other depression among

TCAs users than those prescribed SSRIs or SNRIs. Patients with newly diagnosed depression were the least likely to be prescribed TCAs (Table 7.1).

Treatment outcome

Over the 18-month observation period, 31,466 of the subjects were categorised as having sustained treatment-free status (32.6%), 50,652 (52.5%) were having continuous treatment and 14,383 (14.9%) late re-contacts. Of TCA recipients, 57.6% (the highest proportion among the antidepressant groups) were having continuous treatment while only 28.3% (the lowest among antidepressant groups) of them achieved sustained treatment-free status (Table 7.2).

Unadjusted rates of sustained treatment-free status were lower in subjects with CVD, compared to their counterparts without CVD, with the exception of those prescribed with TCAs. For the latter patients, those with CVD had higher unadjusted rates of sustained treatment-free status (see Table 7.2). After adjusting for other demographic/clinical covariates, people with CVD had lower treatment success rates regardless of antidepressant groups (Table 7.3). As shown in Table 7.3, SSRI recipients had the highest adjusted rates of treatment success and QALYs accrued regardless of baseline comorbid CVD (Table 7.3).

Costs

Table 7.2 shows that in general, patients with comorbid CVD had lower psychiatric costs but higher total costs than those without CVD. Regarding treatment groups,

SNRIs users had both the highest psychiatric and total costs over the 12-month period followed by those receiving SSRIs and then TCAs, regardless of comorbid CVD.

Cost-utility

From the perspective of psychiatric services, the ICERs showed that SSRIs dominated SNRIs for the full sample while the ICER was 51 international dollars (psychiatric cost; 1,042 NTD) per one percentage point increase in rates of sustained treatment-free status for SSRIs over TCAs; for SNRIs over TCAs, the ICER was 223 international dollars (4,556 NTD). The ICUR for SSRIs over TCAs in the full sample was 67,333 international dollars (1,375,613 NTD) per one additional QALY (Table 7.3).

For those with CVD, there was an incremental cost of 53 international dollars (psychiatric costs) to gain one percentage point increase in rates of sustained treatment-free status for SSRIs over TCAs, while SNRIs were dominated by SSRIs (higher costs and worse outcomes). For the non-CVD population the ICER was 59 international dollars (psychiatric costs; 1,205 NTD) per one percentage point increase in rates of sustained treatment-free status for SSRIs over TCAs. For the CVD and non-CVD populations, the ICURs for SSRIs over TCAs were 53,333 (1,089,593 NTD) and 78,333 (1,600,343 NTD) international dollars per one additional QALY gained respectively (Table 7.3).

Table 7.1. Demographic data and baseline characteristics (by comorbid CVD)

	Patients with CVD (n=27,484)				Patients without CVD (n=69,017)			
	SSRI	SNRI	TCA	Statistics	SSRI	SNRI	TCA	Statistics
Age [mean (SD)]	59.18 (16.25)	56.25 (16.26)	61.88 (14.08)	F=125.08, P<.001	42.75 (15.35)	41.32 (14.31)	49.48 (14.87)	F=900.27, P<.001
Male [n (%)]	7658 (39.6)	1288 (37.7)	1889 (40.2)	Value=5.37, p=.068	18281 (36.9)	3610 (36.1)	3730 (39.6)	Value=31.43, P<.001
Other depression [n (%)]	10926 (56.4)	1794 (52.5)	3457 (73.5)	Value=518.18, p<.001	27166 (54.8)	5029 (50.3)	6632 (70.5)	Value=961.85, p<.001
Newly diagnosed depression [n (%)]	5544 (28.6)	779 (22.8)	933 (19.8)	Value=177.11, p<.001	17221 (34.7)	3360 (33.6)	2281 (24.2)	Value=393.57, p<.001
Baseline outpatient visit number [mean (SD)]	46.47 (28.22)	46.15 (27.88)	51.61 (31.66)	F=63.30, p<.001	27.37 (20.50)	27.90 (21.03)	32.27 (23.75)	F=214.91, p<.001
Baseline total healthcare costs [mean (SD)]	4024 (5364)	4063 (5137)	3629 (4856)	F=11.45, p<.001	1783 (3157)	1984 (3066)	1885 (3251)	F=18.85 p<.001

Baseline characteristics were measured over the 12-month pre-index period and costs were expressed in 2002-3 international dollars.
SD=standard deviation; CVD=cardiovascular diseases; SSRI=selective serotonin reuptake inhibitor; SNRI=serotonin norepinephrine reuptake inhibitor; TCA=tricyclic antidepressant.
Chi-squared test was used for comparing categorical variables between antidepressant groups and ANOVA was used for continuous variables.

Table 7.2. Unadjusted costs, treatment outcomes, and QALYs

	Full sample (n=96,501)				Patients with CVD (n=27,484)				Patients without CVD (n=69,017)			
	SSRI	SNRI	TCA	Statistics	SSRI	SNRI	TCA	Statistics	SSRI	SNRI	TCA	Statistics
Psychiatric costs	1101	1628	632	F=869.34,	1009	1499	540	F=275.68,	1137	1672	679	F=581.32,
[mean (SD)]	(1937)	(2473)	(1634)	p<.001	(1865)	(2141)	(1380)	p<.001	(1964)	(2575)	(1746)	p<.001
Total costs	3173	3517	3079	F=26.96,	4850	4970	4342	F=10.10,	2519	3020	2447	F=63.78,
[mean (SD)]	(5466)	(5063)	(5684)	p<.001	(7548)	(7101)	(7264)	p<.001	(4217)	(4026)	(4569)	p<.001
Psychiatric inpatient	284	444	180	F=82.64,	260	379	140	F=20.31,	321	507	218	F=60.05,
care costs [mean (SD)]	(1692)	(2135)	(1410)	p<.001	(1751)	(1820)	(1204)	p<.001	(1833)	(2422)	(1641)	p<.001
Total inpatient care	1018	1050	1027	F=.29,	1885	1775	1647	F=2.54,	780	901	826	F=4.94,
costs [mean (SD)]	(4442)	(4074)	(4533)	p=.748	(680)	(641)	(637)	p=.079	(3614)	(3357)	(3849)	p=.007
Number of treatment	23116	4354	3996	Value=	6054	977	1358	Value=	17062	3377	2638	Value=208.
success [n (%)]	(33.5)	(32.4)	(28.3)	238.12,	(31.3)	(28.6)	(28.9)	46.59,	(34.4)	(33.8)	(28.0)	69, p<.001
Number of late	10600	1795	1988	p<.001	2829	421	616	p<.001	7771	1374	1372	
re-contact [n (%)]	(15.4)	(13.4)	(14.1)		(14.6)	(12.3)	(13.1)		(15.7)	(13.7)	(14.6)	
Number of continuous	35249	7269	8134		10479	2018	2732		24770	5251	5402	
treatment [n (%)]	(51.1)	(54.2)	(57.6)		(54.1)	(59.1)	(58.1)		(49.9)	(52.5)	(57.4)	
Gained QALYs	0.62	0.62	0.63	F=173.32,	0.62	0.62	0.63	F=99.12,	0.62	0.62	0.63	F=86.65,
[mean (SD)]	(0.06)	(0.06)	(0.06)	p<.001	(0.06)	(0.06)	(0.06)	p<.001	(0.06)	(0.06)	(0.06)	p<.001

Costs (over the 12-month period following the index date) were expressed in 2003-4 international dollars.
Treatment success in this thesis was defined as sustained treatment-free status.
SD=standard deviation; CVD=cardiovascular diseases; SSRI=selective serotonin reuptake inhibitor; SNRI=serotonin norepinephrine reuptake inhibitor;

TCA=tricyclic antidepressant; QALY=quality-adjusted life-year
Chi-squared test was used for comparing categorical variables between antidepressant groups and ANOVA was used for continuous variables.

Table 7.3. Adjusted psychiatric costs, treatment outcomes, QALYs and ICER/ICUR*

	Full sample (n=96,501)			Patients with CVD (n=27,484)			Patients without CVD (n=69,017)		
	Mean (95% Wald Confidence Interval)								
	SSRI	SNRI	TCA	SSRI	SNRI	TCA	SSRI	SNRI	TCA
Psychiatric costs	1070 (1057, 1084)	1537 (1506, 1567)	868 (838, 899)	966 (942, 990)	1376 (1320, 1433)	806 (757, 855)	1115 (1098, 1131)	1594 (1558, 1630)	880 (842, 918)
Rate of treatment success	0.32 (0.32, 0.32)	0.31 (0.30, 0.32)	0.28 (0.28, 0.29)	0.30 (0.30, 0.31)	0.29 (0.27, 0.31)	0.27 (0.26, 0.29)	0.33 (0.32, 0.33)	0.32 (0.31, 0.33)	0.29 (0.28, 0.30)
Gained QALYs	.625 (.625, .626)	.624 (.623, .625)	.622 (.621, .623)	.625 (.624, .625)	.623 (.622, .625)	.622 (.621, .623)	.625 (.625, .626)	.624 (.624, .625)	.622 (.621, .623)
	SSRI vs. SNRI	SSRI vs. TCA	SNRI vs. TCA	SSRI vs. SNRI	SSRI vs. TCA	SNRI vs. TCA	SSRI vs. SNRI	SSRI vs. TCA	SNRI vs. TCA
ICER	SSRI dominates	51	223	SSRI dominates	53	285	SSRI dominates	59	238
ICUR	SSRI dominates	67,333	334,500	SSRI dominates	53,333	570,000	SSRI dominates	78,333	358,500

*Costs, outcomes, and QALYs were adjusted for age, gender, mental and physical comorbidities as described earlier in the section of demographic and clinical information; costs were expressed in 2003-4 international dollars.
CVD=cardiovascular diseases; SSRI=selective serotonin reuptake inhibitor; SNRI=serotonin norepinephrine reuptake inhibitor; TCA=tricyclic antidepressant; QALY=quality-adjusted life-year; ICER= incremental psychiatric cost per percentage point of treatment success; ICUR=incremental psychiatric cost per QALY gained.

CEACs were used to interpret the cost-utility results, while demographic/clinical correlates were controlled for. For the full sample, TCAs would be 100% likely to be the most cost-effective option rather than SSRIs and SNRIs if society is willing to pay nothing for an additional gain in QALY (Figure 7.1a based on psychiatric costs, Figure7.1b based on total costs).

Figure 7.1a: CEAC based on psychiatric costs (full sample)

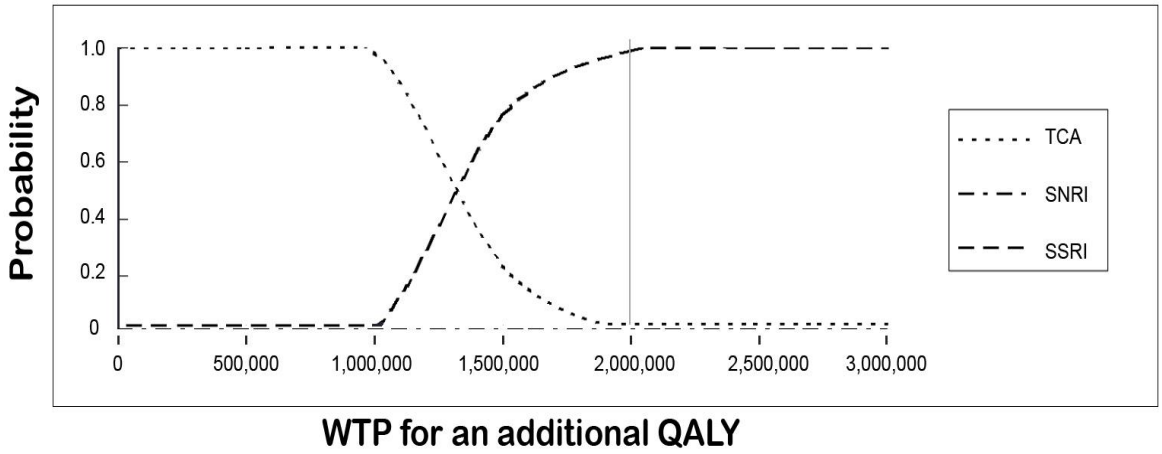
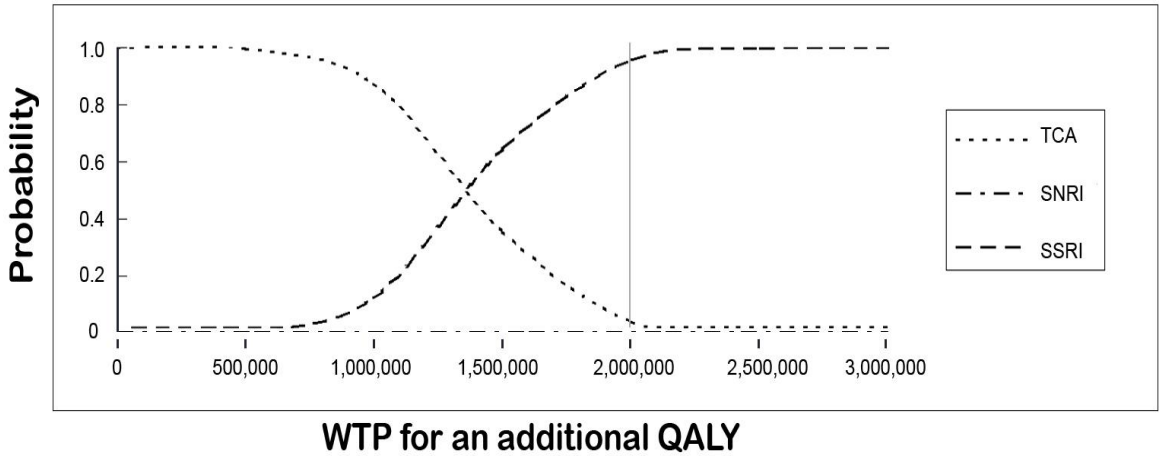


Figure 7.1b: CEAC based on total costs (full sample)

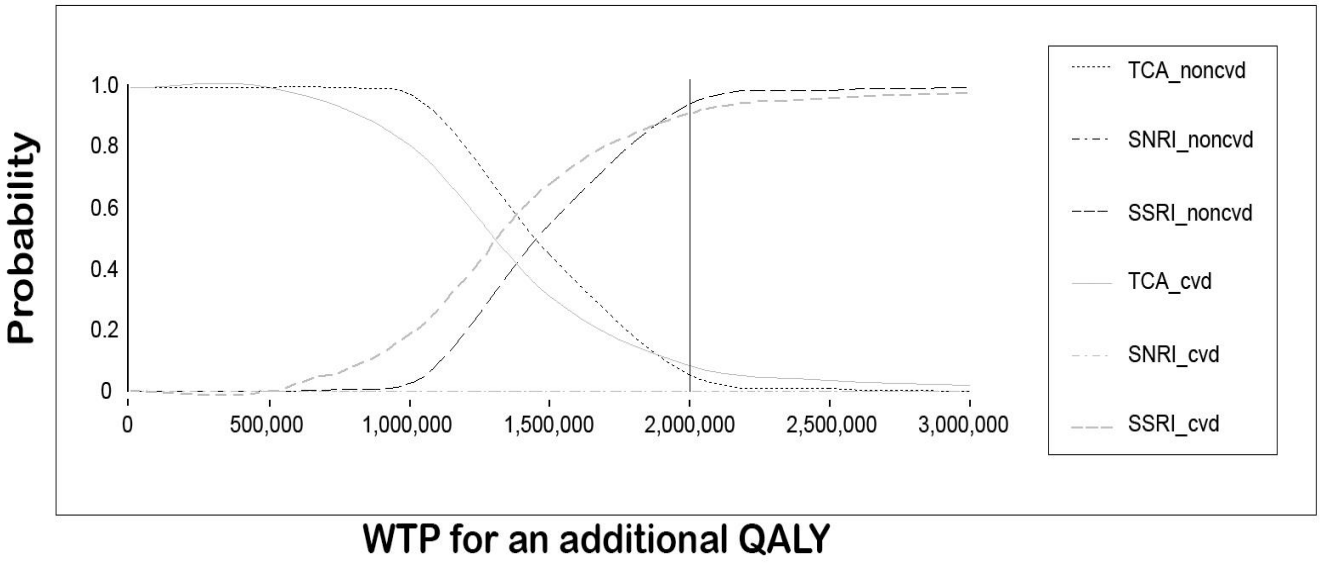


Footnote: The horizontal axis: willingness-to-pay for an additional QALY in the local national currency, NTD. The vertical axis: probability for an antidepressant group of interest to be more cost-effective than the alternatives.

As seen in Figure 7.1, when society is willing to pay NTD 1,500,000 (£30,000) for an additional QALY, there is a 76.4% (psychiatric costs) to 64.5% (total costs) likelihood that SSRIs would be most cost-effective compared to TCAs and SNRIs in patients with depression (the full sample). This is also in accordance with the above results: the ICUR for SSRIs over TCAs in the full sample was 67,333 international dollars (around £30,000) per one additional QALY. Then, if the willingness-to-pay increases to NTD 2,000,000 (£40,000) for an additional QALY, there is a 99.1% (psychiatric costs) to 95.9% (total costs) likelihood that SSRIs are the most cost-effective option compared to TCAs and SNRIs (Figure 7.1).

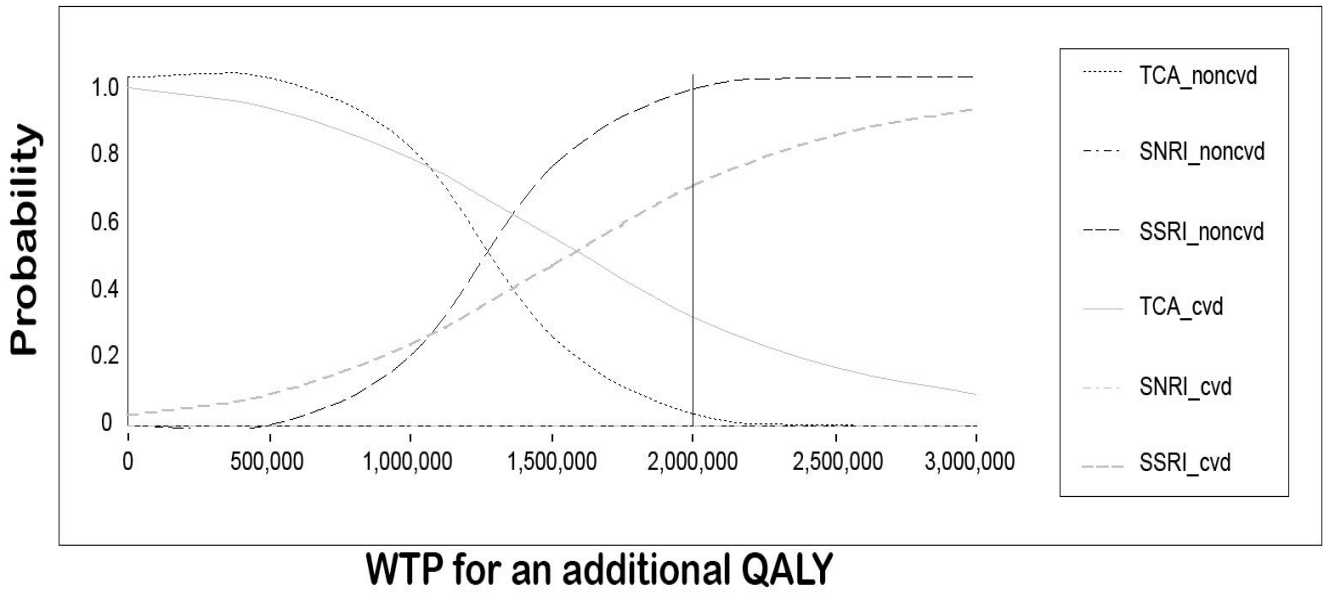
In subgroup analyses shown in Figure 7.2a (CEAC based on psychiatric costs) and 7.2b (CEAC based on total costs), the darker lines represented the CEACs of different antidepressant categories for the non-CVD patients and lighter lines represented those for patients with comorbid CVD (TCA_noncvd: TCA recipients from the non-CVD group; SNRI_cvd: SNRI recipients from the CVD group).

Figure 7.2a: CEAC based on psychiatric costs (subgroup analysis by comorbid CVD)



Regardless of the presence of comorbid CVD, if society is willing to pay nothing for an additional QALY, TCAs would be 100% likely to be the most cost-effective option compared to SSRIs and SNRIs. However, if society is willing to pay NTD 1,500,000 (£30,000) for an additional QALY, there is a 55% (psychiatric costs) to 74.5% (total costs) likelihood that SSRIs would be most cost-effective compared to TCAs and SNRIs for those without comorbid CVD whereas for those with CVD, the figures are 68.9% (psychiatric costs) and 46.1% (total costs), respectively.

Figure 7.2b: CEACs based on total costs (subgroup analysis by comorbid CVD)



Furthermore, if society is willing to pay NTD 2,000,000 (£40,000) - the reported willingness-to-pay threshold for an additional QALY in Taiwan (Shiroiwa et al., 2010) - the likelihood for SSRIs to be the most cost-effective is 94.4% (psychiatric costs) and 96.6% (total costs) in patients without comorbid CVD. The figures are 91.7% (psychiatric costs) and 68.8% (total costs), respectively, in patients with comorbid CVD (Figure 7.2a and Figure 7.2b). Therefore, the higher the value society places on an additional gain in QALY, the greater the net benefit to society from the use of SSRIs over TCAs and SNRIs for both patients with comorbid CVD and those without. At willingness-to-pay values up to NTD 3,000,000, the likelihood of SSRI being most cost-effective are either 100% (psychiatric costs) or approaching 100% (total costs).

Sensitivity analysis

(i) Varying the utility weight for the continuous treatment health state to the highest value of 0.75: As presented in Figure 7.3a to 7.3d, TCAs (the dotted line) had over 90% likelihood of being the most cost-effective option than the other antidepressants up to a willingness-to-pay level of NTD 2,000,000 (Figures 7.3a to 7.3d).

Figure 7.3a. Sensitivity analysis (i): CEAC based on psychiatric costs (for patients without comorbid CVD)

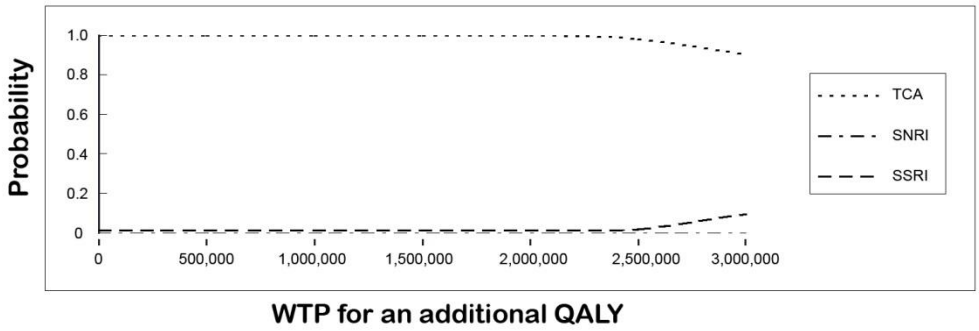


Figure 7.3b. Sensitivity analysis (i): CEAC based on psychiatric costs (for patients with comorbid CVD)

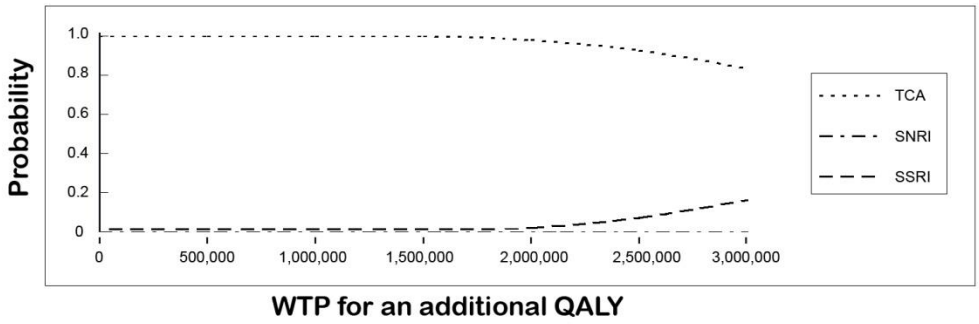


Figure 7.3c. Sensitivity analysis (i): CEAC based on total costs (for patients without comorbid CVD)

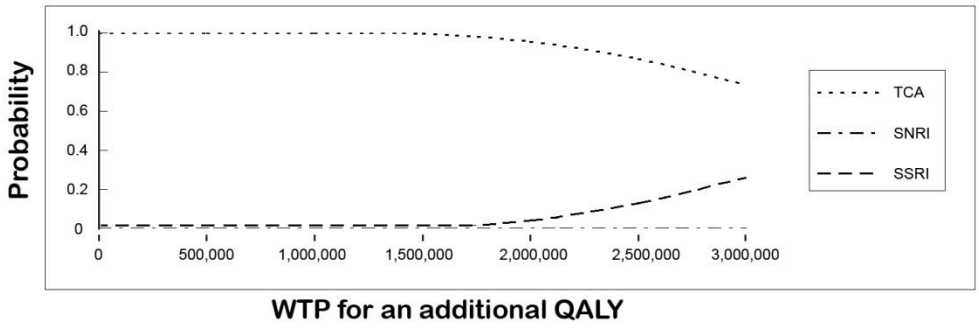
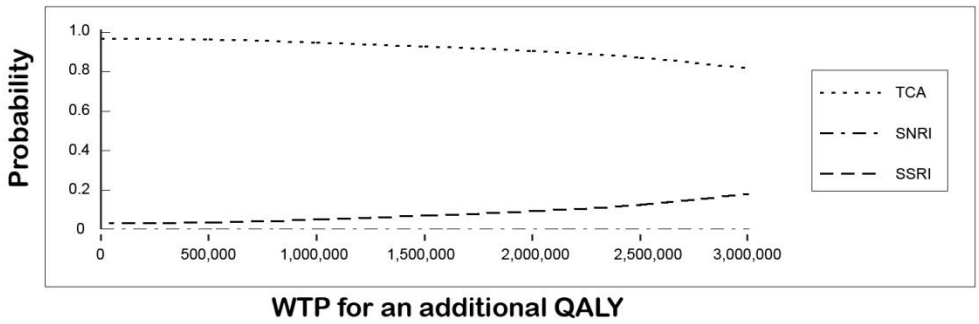


Figure 7.3d. Sensitivity analysis (i): CEAC based on total costs (for patients with comorbid CVD)



(ii) Varying the utility weight for 'continuous treatment' health state to the lowest value of 0.53: For patients without CVD, there is a 100% likelihood that SSRIs would be the most cost-effective option compared to the other antidepressants at the willingness-to-pay level at or over NTD 1,500,000; the probabilities are 99.5% (psychiatric costs) and 94.9% (total costs), respectively, at NTD 1,500,000 for those with CVD (Figures 7.4a to 7.4d).

Figure 7.4a. Sensitivity analysis (ii): CEAC based on psychiatric costs (for patients without comorbid CVD)

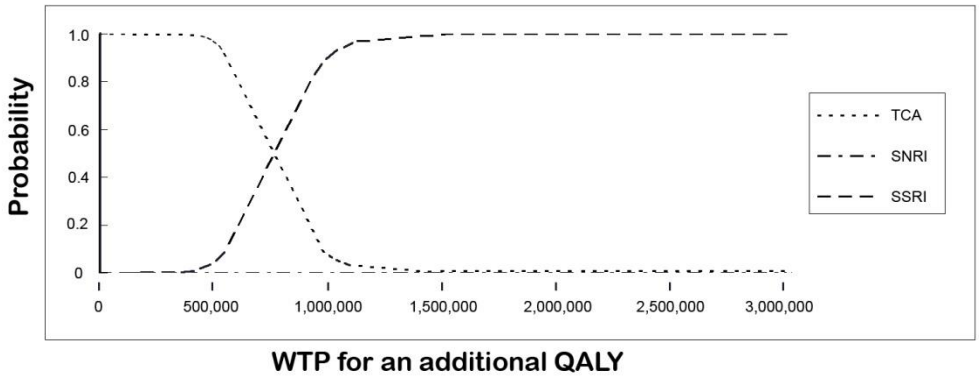


Figure 7.4b. Sensitivity analysis (ii): CEAC based on psychiatric costs (for patients with comorbid CVD)

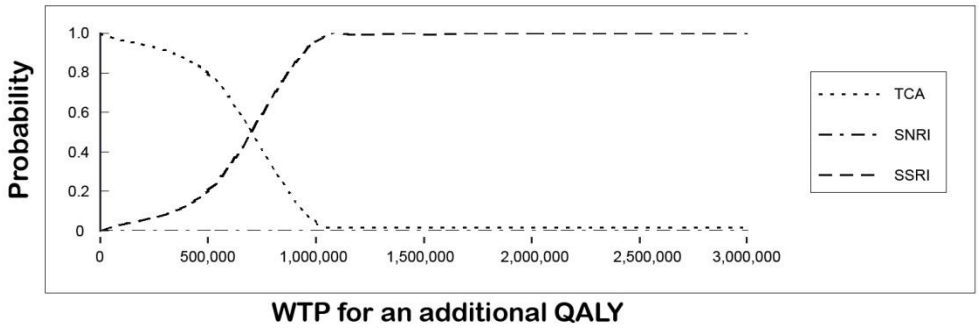


Figure 7.4c. Sensitivity analysis (ii): CEAC based on total costs (for patients without comorbid CVD)

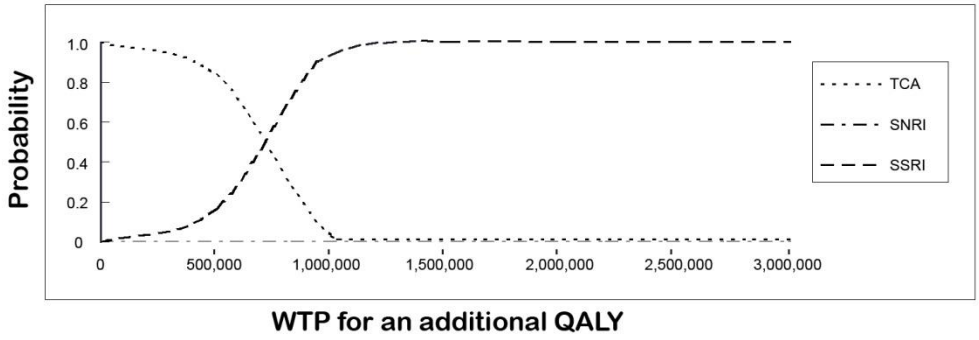
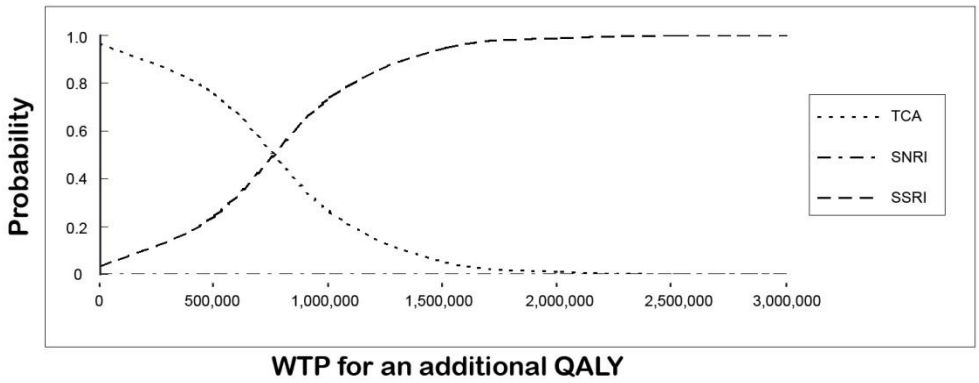


Figure 7.4d. Sensitivity analysis (ii): CEAC based on total costs (for patients with comorbid CVD)



(iii) Varying the utility weight for the late re-contact health state to the baseline value of 0.42 for those with MDD and 0.60 for those with other types of depression: At the willingness-to-pay level of NTD 1,500,000, SSRIs start to gain advantage over TCAs (Figures 7.5a to 7.5d).

Figure 7.5a. Sensitivity analysis (iii): CEAC based on psychiatric costs (for patients without comorbid CVD)

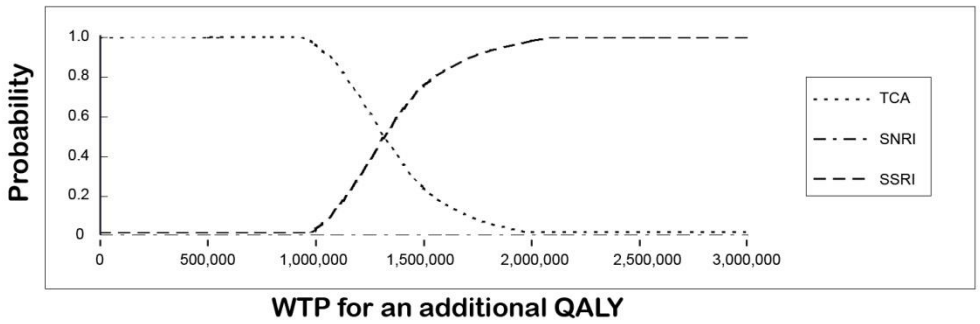


Figure 7.5b. Sensitivity analysis (iii): CEAC based on psychiatric costs (for patients with comorbid CVD)

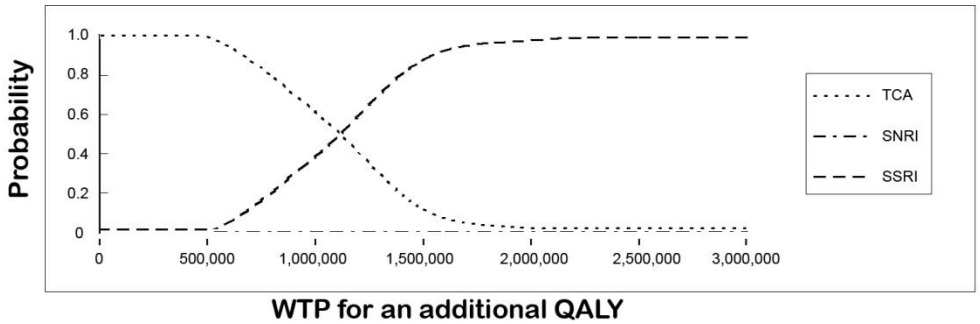


Figure 7.5c. Sensitivity analysis (iii): CEAC based on total costs (for patients without comorbid CVD)

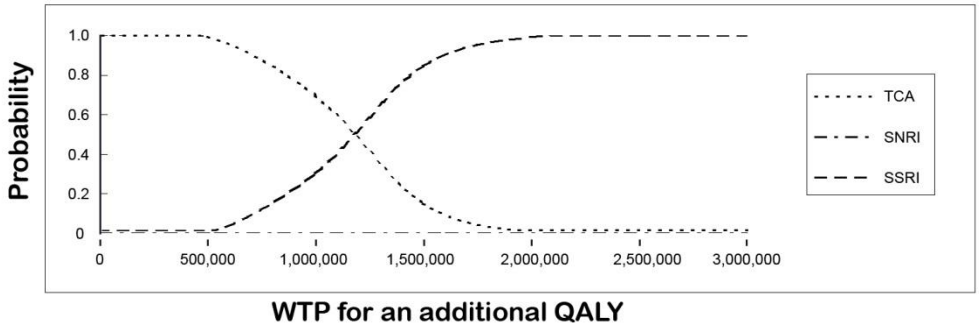
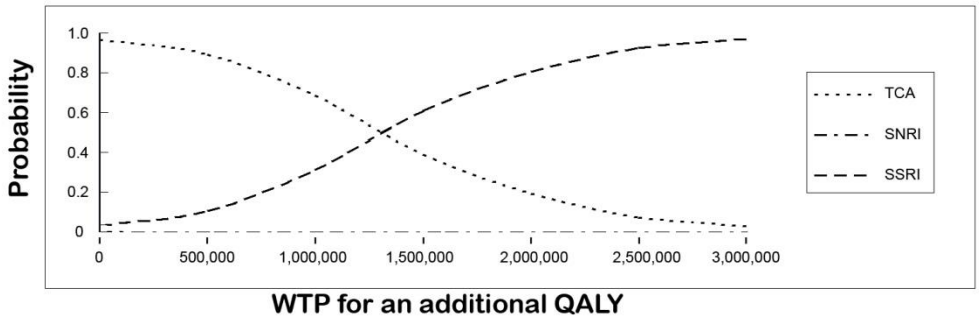


Figure 7.5d. Sensitivity analysis (iii): CEAC based on total costs (for patients with comorbid CVD)



(iv) Varying the utility weight for the late re-contact health state to a lower value of 0.27: In Figures 7.6a to 7.6d), SSRIs gained advantage of being more cost-effective when willingness-to-pay values were at or over NTD 2,000,000 with the exception of patients with CVD (total costs, see Figure 7.6d): At a willingness-to-pay level up to NTD 3,000,000, the likelihood is 66.5%.

Figure 7.6a. Sensitivity analysis (iv): CEAC based on psychiatric costs (for patients without comorbid CVD)

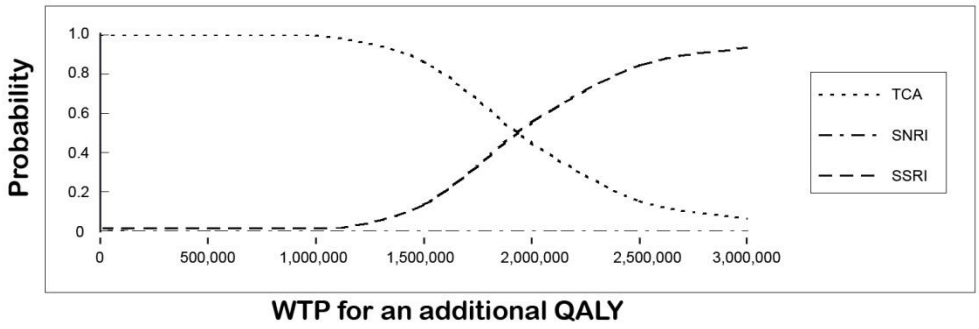


Figure 7.6b. Sensitivity analysis (iv): CEAC based on psychiatric costs (for patients with comorbid CVD)

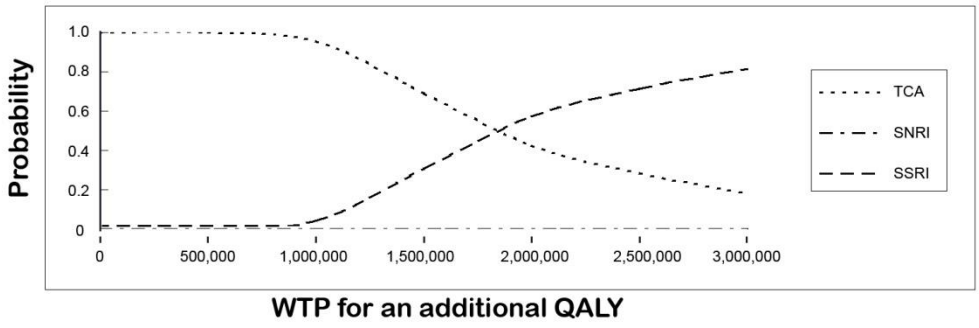


Figure 7.6c. Sensitivity analysis (iv): CEAC based on total costs (for patients without comorbid CVD)

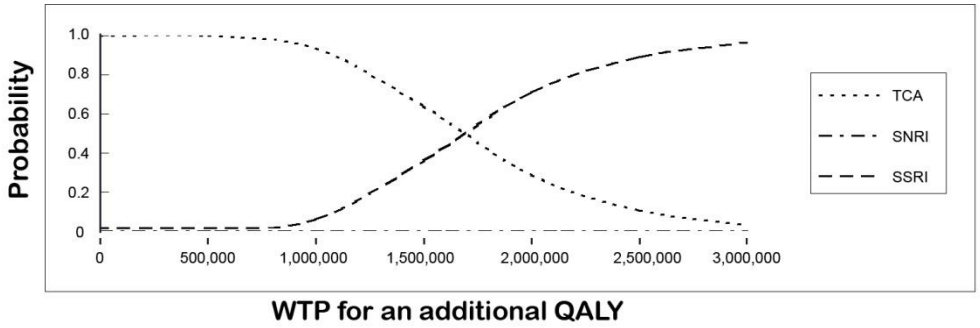
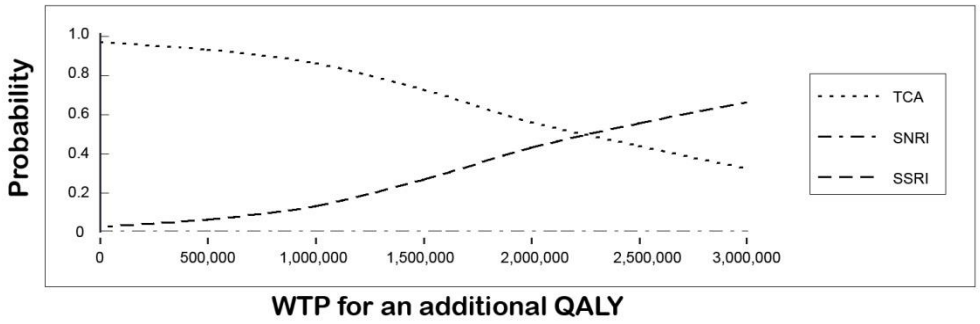


Figure 7.6d. Sensitivity analysis (iv): CEAC based on total costs (for patients with comorbid CVD)



7.4. Discussion

The analyses presented in this chapter have provided information comparing the cost-effectiveness and cost-utility of individual antidepressant classes and have examined the impact of CVD. In the whole sample, the ICERs showed that SSRIs dominated SNRIs and the ICER was 51 international dollars (psychiatric cost; 1,042 NTD) per one percentage point increase in rates of sustained treatment-free status for SSRIs over TCAs. The ICUR for SSRIs over TCAs in the full sample was 67,333 international dollars (1,375,613 NTD) per one additional QALY. For the CVD and non-CVD populations, the ICURs for SSRIs over TCAs were 53,333 international dollars (1,089593 NTD) and 78,333 (1,600,343 NTD) per one additional QALY gained respectively (Table 7.3).

In the CEACs, SSRIs were shown to be more cost-effective compared to TCAs and SNRIs at a willingness to pay of NTD 1,500,000 for an additional QALY. The CEACs showed differences in cost-utility between antidepressant treatments by comorbid CVD. For patients without CVD, SSRIs were clearly most cost-effective but for those with comorbid CVD, the advantage of SSRIs over TCAs seemed relatively modest. These results add to the literature by providing such information at the population level rather than for groups of patients meeting the specific criteria for trials.

Some previous studies have shown that SSRIs may improve quality of life more than TCAs for patients with depression (Taylor et al., 2011). The analyses here suggest that such gains may be achieved in a cost-effective way by showing that when willingness-to-pay increases (but remains below the threshold), the probability for

SSRIs to be more cost-effective in improving patients' quality of life increases. From the perspectives of healthcare providers, the results are in accordance with a previous cost-utility study (Kendrick et al., 2006) in finding that SSRIs are more cost-effective in improving quality of life in routine clinical settings. To date, only a very limited number of prospective studies have been conducted to address the cost-utility of antidepressant treatments and the findings are inconclusive. The aforementioned study has suggested SSRIs may be more cost-effective than TCAs but only with a probability of up to 0.6 (Kendrick et al., 2006) while elsewhere it has been suggested that imipramine (a TCA) dominates fluoxetine (a SSRI) with 81.5% of the bootstrap replications in the quadrant of the cost-effectiveness plane indicating dominance (Serrano-Blanco et al., 2009). There are different explanations for the inconsistency between previous results. Two key issues are the differences in cost perspectives adopted and the fact that the sample sizes of these studies are small, thus leaving the cost-effectiveness results unstable with wide confidence intervals. In this thesis the perspective was still relatively limited but the sample size of this national cohort was substantial. Analyses were conducted controlling for potential demographic/clinical confounders which makes the results relatively robust.

Moreover, these analyses have also addressed cost-utility differences of antidepressant treatments in patients with comorbid depression and CVD, something not been previously studied. Depression has been suggested as an independent risk factor for the future onset, progression, and recurrence of CVD (Carney et al., 1988; Ferketich et al., 2000; Nicholson et al., 2006; Rugulies, 2002; Sesso et al., 1998; Wassertheil-Smoller et al., 2004). There is also evidence suggesting that factors related to CVD might influence outcomes of depression (Albus et al., 2011; Denollet

et al., 2010). Given that both depression and CVD are very prevalent conditions and leading causes of disease burden (WHO, 2008), the importance of in-depth investigations into their effects cannot be over-emphasised. The findings that SSRIs can be more cost-effective than TCAs and SNRIs in both patients with and without comorbid CVD could serve as useful information for guiding depression management in the presence of CVD in clinical settings.

However, the finding that SSRIs have a relatively modest advantage over TCAs in patients with CVD (compared to patients without CVD) appears counterintuitive at first sight. Because TCAs have been shown to be associated with a variety of cardiovascular effects (Coupland et al., 1997; Taylor, 2008; Vieweg and Wood, 2004), it would be expected that treatment with TCAs may be related to higher costs assuming the same efficacy and more adverse effects. Yet the reality appears to be the opposite. There are explanations for this phenomenon among which physician choice could play a critical role. In a previous cost-utility study, a higher proportion of patients randomised to TCAs were in fact prescribed a different class of antidepressants than those randomised to SSRIs (TCA: 42% vs. SSRI: 16%) and physician preference was the stated cause for over half of these cases who did not receive the allocated treatment (Kendrick et al., 2006). It is understandable that instead of TCAs, physicians may tend to prescribe SSRIs to patients with more complicated physical conditions, including CVD. As a result, the QALY gains used in the estimates of net benefits for those SSRIs users might be offset by increased costs due to more complicated physical conditions. This may be reflected in Figure 7.2 where for individuals with CVD, SSRIs were shown to be more cost-effective (compared to TCAs) in the model estimated using psychiatric costs than in that using

total costs. The higher non-psychiatric costs of those SSRIs users, even after adjusting for age and severity of depression, may diminish the cost-effectiveness advantage over TCAs in the model using total costs.

In this chapter, SSRIs were shown to be more likely to be cost-effective in most scenarios covered by the sensitivity analyses. An exception (sensitivity analysis (i)) is when the 'continuous treatment' utility score is changed to 0.75; TCAs then become the most cost-effective choice. This implies that the utility scores for the 'continuous treatment' health state is a major driver of the cost-utility results. Since TCA users had the highest proportion of being on continuous treatment (57.6%) between antidepressant groups (51.1% of SSRI users were having continuous treatment - the lowest proportion between groups, see Table 7.2), varying utility scores for the 'continuous treatment' health state to the highest level would naturally favour TCAs. Nonetheless, it seems unlikely that a heterogeneous group of people on continuous treatment would have a mean utility higher than for the responders/non-remitters health state of 0.72. Depression severity has been shown to impact utility scores (Sapin et al., 2004; Sobocki et al., 2007) and patients with moderate or severe depression are the most likely to be on continuous treatment given their relapsing/chronic disease nature. From the available observational studies following depressed patients in clinical settings, Gunther et al (2008) reported a mean EQ-5D index UK score of 0.65 (n=104) at 18-months follow up and Reed et al (2009) also suggested a nearly identical EQ-5D value at six-months follow up based on a sample of 3468 adult patients with a clinically diagnosed episode of depression after commencing antidepressant treatment. Hence, the utility score 0.66 applied in the base model (Sobocki et al., 2007) may be the most appropriate estimate for the current

analysis and the finding that SSRIs are more cost-effective appears valid.

The issue to be raised herein is the level of quality of life for patients on continuous treatment. In this chapter, a high (52.5%) percentage of patients had a treatment outcome status of being on continuous treatment. Despite efforts to improve treatment outcomes of depression, only 12-18% of patients with MDD who receive antidepressant treatment may achieve complete symptom remission and full functional recovery (Fava et al., 1994; Gasto et al., 2003; Israel, 2010; Nierenberg et al., 1999). As a result, the majority of patients can be on continuous treatment for a long period of time. However, most previous studies used hypothesised contexts and questions to generate utility scores and there has been no population-based study specifically examining utility scores for patients who are on continuous treatment over a longer term in real-world settings. Future in-depth investigations of patients' quality of life when receiving treatment in clinical settings are warranted to further improve depression management and patients' quality of life.

7.5. Limitations and implications

There are various limitations to be considered in these analyses. The adoption of utility scores from previous studies is a major one. Whether utility values from different settings (and countries) can be adequately applied to other study settings is a concern because preference values towards health states have been shown to differ between countries (Badia et al., 2001; Johnson et al., 2005). The current analysis adopted utility values of depressive health states from other countries under the assumption that changes in utility values between health states of depression (for

instance, remission or relapse) would be similar despite the presence of differences in the absolute utility values across countries (also see Section 5.6). Although sensitivity analyses based on different assumptions for these utility scores were conducted to confirm the validity of the results from the base model, the limitation due to the use of social preference values elicited from a different country should still be noted. Future research to obtain utility weights for patients with depression in Taiwan is warranted to validate the current results. Besides, since the perspective of healthcare providers for the economic analysis was adopted in this chapter, it was unable to examine wider effects. The strength of this analysis is the large sample size, good representativeness (whole country coverage), and the complete cost data. In addition, availability of willingness-to-pay data from Taiwan renders the results more interpretable.

Implications for practice

The finding that at the threshold willingness-to-pay value, SSRIs are more cost-effective than TCAs and SNRIs in patients with and without comorbid CVD suggests that SSRIs can be the first choice of treatment in routine clinical settings to improve both treatment effectiveness and patients' quality of life in Taiwan. Although the advantage seems relatively modest in patients with CVD, considering the apparent safety of SSRIs in patients with CVD (Taylor et al., 2011) and the demonstrated cost-effectiveness and cost-utility in this chapter, SSRIs can be considered a better choice of antidepressant treatment for patients with comorbid CVD.

Chapter 8. Discussion and conclusions

The aims of this thesis were to examine the background to depression treatment and the impact of antidepressant treatment and comorbidities on economic costs (Chapter 1), to undertake a systematic review of published economic evaluations of antidepressant treatments for depression and to identify appropriate evaluation approaches and gaps in the methodology (Chapter 2), to critically appraise the methods of economic evaluation as applied to evaluations of antidepressant treatments (Chapter 3), to report results of the analysis of costs of antidepressant treatment for patients with depression (Chapter 4), to identify appropriate effectiveness and utility measures for the cost-effectiveness and cost-utility analyses (Chapter 5), to assess the impacts of treatment outcomes on costs over the following three years (Chapter 6), and to compare the relationship between cost and effectiveness/utility measure between antidepressant treatments (Chapter 7). All of the analyses in this thesis were conducted using healthcare data from Taiwan.

The purpose of this discussion chapter is to pull together the findings that relate to the above aims. It will begin by summarising findings from the previous chapters followed by a discussion of the implications and main limitations. Finally, directions for future research will be suggested.

8.1. Summary of findings

Study design

In Chapter 3, the appropriateness of different study designs for an economic evaluation of antidepressant treatments was considered. Using Black's list (Black, 1996) of circumstances when randomisation is *not* appropriate, it was concluded that there may be a number of characteristics of the issues being addressed here that would make a randomised design difficult to apply and a database approach potentially more appropriate. For instance, an important issue is the need for the compliance and co-operation of patients and physicians. Preferences and other factors may influence physicians' choice and patients' adherence to antidepressants. Besides, because the aim of this thesis is to assess cost-effectiveness in routine settings, it is difficult to conduct a RCT without minimally interfering with behaviours of daily practice.

Outcomes

The relationship between the choice of outcome measure and study design used in economic evaluations was considered. Subsequently, a database definition of treatment outcome (Pan et al., 2013c), including sustained treatment-free status, late re-contact, and continuous treatment, was introduced in this thesis, rather than specifically using remission (Sicras-Mainar et al., 2010a) as an effectiveness measure (Chapter 5). Utility weights were attached to these different outcomes to conduct the cost-utility analysis presented in Chapter 7.

From the very beginning, it was considered that over the past decades, it has become increasingly recognised that responding to depression treatment but failing to achieve full remission can be an adverse outcome (Anderson et al., 2000; Ballenger, 1999). The consequences of not achieving full remission can lead to greater risk of relapse/recurrence (Judd et al., 2000; Ramana et al., 1995), more frequent depressive episodes and shorter periods between episodes (Judd et al., 2000); it may even lead to increased mortality and morbidity (de Groot et al., 2001; Empana et al., 2005; Ickovics et al., 2001). Conversely, treating to remission is shown to be beneficial to long-term outcomes. For example, it is associated with a reduced risk of relapse and improved psychosocial functioning (Judd et al., 2000; Miller et al., 1998; Thase et al., 1992). Therefore, where possible, the key goal of an intervention should be remission - complete relief of symptoms, which is linked to better functioning and a lower likelihood of relapse (Kennedy and Foy, 2005).

Although remission is a desired treatment goal for depression treatment, the necessary clinical data were not collected for ascertaining a remission as defined by clinical rating scale criteria. Hence, it was necessary to consider the specific issue of identifying an appropriate effectiveness or utility outcome measure for use in economic evaluations based on a database approach. An alternative term, treatment-free status (Pan et al., 2013c), was deemed more suitable, rather than a database-defined ‘remission’, and was employed in this thesis for all analyses. While sustained treatment-free status was not technically ‘remission’, it may indicate initial treatment effectiveness without later clinical fluctuations sufficient to trigger a medical contact. In effect then, the measure used in the thesis and ‘actual’ remission may amount to the same thing.

Because depression is associated with marked decreases in functioning, well being and health-related quality of life (Hays et al., 1995; Saarijarvi et al., 2002), and increases in disability days (Lecrubier, 2001), it is important to evaluate economic impacts of interventions to depression using quality of life data. Recent research suggests that the importance of using utility measures is not only because it can be compared between treatments from different fields, which matters to decision makers, but also because depression can seriously impact individuals' quality of life in varied ways. In Chapter 5, methods for valuing health states and obtaining data for deriving utility values for health states of patients with depressive disorders were summarised.

Results of cost analysis

In Chapter 4, results of the cost analysis were presented with a particular focus on factors influencing the costs of depression treatment, e.g. past treatment history, comorbid physical illnesses, painful physical symptoms, and choice of initial antidepressants. The cohort of adult cases (n=216,557) who received treatment for depression was identified from the National Health Insurance Research Database. Factors associated with service use and healthcare costs over a 12-month period were explored using generalised linear modelling. The results showed that depression severity, past treatment history, comorbid mental/physical illnesses, painful physical symptoms, and choice of initial antidepressants were found to be associated with healthcare costs in the following year, but the nature of the associations differed across cost categories (e.g. newly diagnosed depression or an initial prescription of a TCA was shown to be associated with higher non-psychiatric costs but lower psychiatric costs). The presence of comorbid cardiovascular disease (CVD) or certain

painful physical symptoms (PPS) at baseline was associated not only with higher non-psychiatric but also with higher psychiatric costs. Further logistic analyses showed that patients with these comorbidities had increased use of psychiatric emergency and inpatient services. Therefore, healthcare costs for depression can be affected by a number of clinical characteristics and comorbidities of patients.

Impact of initial treatment outcome on costs

In Chapter 4, treatment costs for patients with depression over the one year period following initial treatment were compared between groups defined by treatment outcomes, i.e. sustained treatment-free status, late re-contact, or continuous treatment. In Chapter 6, the aim was to identify demographic and clinical characteristics associated with these outcomes after initial treatment and to test whether and how these outcomes influence total healthcare costs over the subsequent three years. In a cohort of adult patients (n=126,471) who received at least three antidepressant prescriptions within the first three months of the index date, factors associated with the above outcomes were examined. Among them, 34.1% were classified as having sustained treatment-free status, 56.6% were continuously on antidepressant treatment, and another 9.4% had cessation of antidepressants for six months and had late re-contacts during the observation period. Potential predictors of total healthcare costs in the subsequent years were assessed via generalised linear modelling, with a particular focus on outcome status after initial treatment. The results showed that depression severity, past treatment history, physician specialty, choice of antidepressants, and comorbid mental/physical illnesses or painful physical symptoms were associated with outcomes after initial treatment. Furthermore, initial outcome

status was shown to affect total healthcare costs over the following three years. Specifically, patients who experienced sustained treatment-free status after initial treatment were found to have significantly lower costs in the second and third years after the index date, compared to those with less favourable outcomes.

Cost effectiveness and cost utility analyses

Since the literature review in Chapter 1 as well as the analyses in earlier chapters indicated that there is an impact of physical comorbidities on economic outcomes for depression, the effect of comorbid CVD on patients' quality of life during the course of depression treatment, and the cost-effectiveness of that treatment, were explored in Chapter 7. Subgroups of adult patients prescribed with antidepressants of interest (SSRIs, SNRIs, and TCAs) for depression were identified. A cost-effectiveness analysis and a cost-utility analysis were conducted comparing antidepressant treatments with and without the presence of comorbid CVD. The results from ICERs and ICURs showed that SSRIs are more cost-effective than TCAs and SNRIs in improving rates of treatment success as well as accrued QALYs. Moreover, the cost-effectiveness acceptability curves (CEACs) showed differences between antidepressant treatments according to CVD status. For patients without CVD, SSRIs were clearly more cost-effective than TCAs and SNRIs but for those with comorbid CVD, the advantage of SSRIs over TCAs was relatively modest.

8.2. Implications

While randomised designs are useful in minimising bias and often acknowledged as

the highest quality comparative design, they are not appropriate for evaluating every study question. It is also difficult to conduct a randomised controlled trial in clinical settings without minimally interfering with routine practices. Therefore, a database analysis is particularly useful in complementing the findings from randomised controlled trials.

Despite the difficulties involved in choosing the outcome measures in the current database analyses, the results suggest they were able to sufficiently capture some elements of the impact of the antidepressant treatments in patients with depression. Furthermore, the initial outcomes (as exemplified by treatment patterns like sustained treatment-free status, late re-contact and continuous treatment) of antidepressant treatment are shown to be affected by demographic and clinical characteristics of patients with depression and these outcomes can have a sustained impact on individuals' total healthcare costs over subsequent three years. Patients who experienced sustained treatment-free status from initial treatment may have significantly lower costs in the second and third years after the index date, compared to those with other outcomes.

The importance of comorbid pain and CVD in terms of influencing treatment costs of depression as shown in Chapter 4 warrants further research. In Chapter 7, SSRIs are shown to be more cost-effective (in ICERs and ICURs) in improving both rates of treatment success and accrued QALYs than TCAs and SNRIs regardless of the comorbid CVD. Although the CEACs showed that the advantage of SSRIs over TCAs is relatively modest in patients with CVD, considering the apparent safety of SSRIs in patients with CVD and the demonstrated cost-effectiveness in improving quality of

life in this thesis, SSRIs can be considered a better choice of antidepressant treatment for patients with comorbid CVD. Since comorbid painful physical symptoms are shown to affect treatment costs for patients with depressive disorders as well, it is worthwhile to further evaluate its influence on cost-effectiveness and cost-utility of depression treatment.

8.3. Limitations

In this thesis, the perspectives of healthcare providers were adopted for all economic analyses. As service use data contained in the National Health Insurance Research Database (NHIRD) includes only health services provided by the National Health Insurance (NHI) system in Taiwan, the perspective of the current analysis was relatively limited, and it was not feasible to analyse wider economic impacts. Future database research may be conducted including proxy measures of employment status to address the impact of treatment on employment as well.

Confounding or selection bias due to the non-randomised study design should always be borne in mind while interpreting the results. Although multivariable analyses were used in this thesis, some bias may remain. Future studies may consider the propensity score methods to remove the effects of confounding when estimating the effects of treatment on outcomes. A proxy measure of outcome status is adopted in these analyses. Despite that this proxy measure has been tested for its concordance with remission determined by clinical criteria and the level of concordance between the two approaches considered acceptable (Cronbach's alpha 90.6%; 95% CI: 85.6, 95.6) (Sicras-Mainar et al., 2010a), the lack of information on clinical symptoms in the

current database is clearly an important limitation.

Additionally, the adoption of EQ-5D tariffs elicited in a different country to assign utility values to Taiwanese patients is another limitation. It should be borne in mind that people in different countries may differ in preferences towards health states due to ethnic, cultural, and socio-economic variations across countries. Although sensitivity analyses based on different assumptions of utility scores were conducted to confirm the validity of results from the base model (in Chapter 7), future efforts to obtain utility values of depressive health states from the Taiwanese populations are needed.

Generalisability is another concern given the unique healthcare system in Taiwan which allows patients to bypass referrals by general practitioners and freely access to specialists care in Taiwan. Caution should be exercised while generalising current results unto different settings or countries.

8.4. Implications for future research

The thesis has highlighted areas which should be the focus of future research (not restricted to database analyses):

1. Care must be taken to ensure that the choice of study design is suitable for the setting and the research question addressed.

2. Care must be taken to ensure that the choice of appropriate outcome measures is

relevant to the research question.

3. Care must be taken to ensure the use of adequate methods to remove the effects of confounding when estimating the effects of interventions on outcomes using database analyses.

4. The validity of database-based outcome measure (e.g. remission or sustained treatment-free status) should be further examined and other potential outcome measures should be searched. Identification of adequate outcome measures, including intermediate outcome measures, may help facilitate future understanding of the relationship between outcomes of depression and costs of treatment.

5. Given that utility scores (or quality weights) of different health states of depression on individual level are still lacking, it is important that further efforts should be placed upon collecting utility data as well as outcomes and costs for patients with depression in different settings and across countries.

6. Although including treatment costs only may be an opportunity to simplify what can be a complicated costing method, wider economic perspectives should be applied in future research to further the understanding of economic impacts of depression treatment.

7. Combination of cost-effectiveness and cost-utility analyses in a study may help interpret the results in a relatively complete way. It is good practice to present the results based on a clinically-relevant effectiveness measure initially and then

undertake a cost-utility analysis as presented in this thesis.

8. Future research should further address the economic impacts of major physical comorbidities and different pain conditions, e.g. headache (Chapter 4), on depression treatment.

9. Economic evaluations addressing newer antidepressants or other modalities of treatments for depression should be emphasised.

10. Economic evaluations addressing cost and outcomes for longer-term follow-up are required.

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Review

Cost-effectiveness comparisons between antidepressant treatments in depression: Evidence from database analyses and prospective studies

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ABSTRACT

Background: Knowledge regarding the relative cost-effectiveness of different antidepressants is crucial for the planning of depression treatment. However, there have been only a small number of reviews of such evidence and synthesizing economic evidence across studies is methodologically challenging. In particular, there have been few reviews of the methods employed in database analyses (studies that use data from real-world practice).
Methods: Published economic evaluations based on database analyses were systematically reviewed to compare antidepressant treatments in depression. Prospective studies of cost-effectiveness were also reviewed to highlight unanswered questions through comparisons between these two different study designs.
Results: Forty papers met the criteria and were included. A relatively large number of industry-sponsored evaluations of escitalopram were identified and these found escitalopram to be potentially cost-effective in depression treatment. Evidence of cost-effectiveness differences between other individual SSRIs was not unequivocally established. Inconsistent findings further emerged concerning the cost-effectiveness of SSRIs versus TCAs between retrospective database analyses and prospective studies.
Limitations: Different outcome measures and cost perspectives make it difficult to make comparisons across studies.
Conclusions: Evidence regarding the cost-effectiveness of different antidepressants in depression continues to accumulate. Beyond the efficacy or tolerability data found for newer antidepressants in controlled trials, further research from real-world settings is needed to examine the relative cost-effectiveness of different antidepressant agents.

Contents

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1. Introduction

Depression is a severe and pervasive disorder. With an estimated lifetime prevalence of 10–25% among women and 5–12% among men (Moore and Bona, 2001), unipolar depressive disorder was the fourth leading cause of burden among all diseases in 2002 and its impact will continue to grow in future decades (Mathers and Loncar, 2006). It is predicted that unipolar depressive disorder will become the leading cause of disease burden by 2015 (WHO, 2008). Given its marked personal, social and economic impacts, depressive disorder creates significant demands on individuals, health service providers and society as a whole (NICE, 2009; Thomas and Morris, 2003).

Although pharmacological, psychological and case management interventions are all recommended, antidepressant drugs remain the mainstay of treatment for depression for most people in contact with healthcare services (Ellis, 2004; NICE, 2009). The last 20 years have seen dramatic changes in antidepressant prescription patterns. Initially, there was an increase in the use of the selective serotonin reuptake inhibitors (SSRIs), which resulted in a progressive rise in total drug expenditures for antidepressants (Barbui et al., 2001; Eccles et al., 1999). Subsequently, other novel antidepressant agents with different pharmacological mechanisms entered the market. Given the range of choices, clinicians must decide about which is the most appropriate intervention for their patients (Simon et al., 1996).

To this end, knowledge regarding the relative cost-effectiveness of individual antidepressants is important. In contrast to the ample evidence on efficacy and tolerability of antidepressant treatments from randomized controlled trials (RCTs), data specifically addressing cost-effectiveness in real-world settings are surprisingly scarce (Brunoni et al., 2009; Montgomery et al., 2005). At the same time, the clinical meaning of the statistical differences in the efficacy or tolerability in RCTs remains uncertain (Cipriani et al., 2005,2009) because study settings and populations of RCTs are principally protocol-driven and operate strict inclusion criteria. This lack of external validity makes it difficult to generalize results to the context of routine medical practice.

Given the gap in knowledge from real-world settings, database analyses using information from actual clinical practice might provide valuable insights into depression treatments for more heterogeneous populations to complement evidence from controlled trials. These studies utilized large administrative databases such as medical claims that captured patients' resource utilization. However, the methodological approaches employed in economic evaluations using database analyses have been diverse and there have been few reviews of their strengths and limitations. The aim of this paper is to systematically assess methodological approaches used in retrospective database analyses of the cost-effectiveness of antidepressant agents in depression treatment. For comparative purposes, economic evaluations from prospective studies are also reviewed to illustrate differences in methodological approaches.

2. Methods

2.1. Search strategy

Studies were identified through a Medline, PsycInfo, and Embase electronic search performed with no limits in language but with limits to human studies ranging from the year 1999 to the present; the final search date was 3 September 2010. Three sets of key words included: cost or cost effectiveness or cost benefit or cost utility or cost consequence or comparative effectiveness; antidepressant; depression or depress$ or major depressive disorder. Reference lists of included papers and previous reviews were hand-searched for published reports missed by the electronic search. Unpublished studies/gray literature were not searched in this review.

2.2. Inclusion criteria

A structured form was designed to record the eligibility of the selected papers from the electronic search. All located papers were first screened by reviewing the titles. The review was initially performed by one author (YPan) with a review of this by another author (PMcCrone) to identify potentially relevant studies. When it was not clear whether a particular study should be included, the full paper was reviewed to ensure eligibility. No limitation on the age of study subjects was

applied. Articles had to meet the following criteria to be included in the review:

1. Comparative analysis of alternative antidepressant treatments (or antidepressant versus placebo) for depressive disorders.
2. Studies undertaken based on a database analysis, an RCT (either conventional or pragmatic), or a naturalistic observational study.
3. Economic evaluations, including cost analysis, cost-effectiveness analysis, cost-benefit analysis, cost-utility analysis, and cost-consequence analysis.
4. Published studies in peer-reviewed journals.

2.3. Data extraction

A structured form was used for the extraction of information on the year of publication, study design, study perspective, length of follow-up, country and setting of the study, antidepressants compared, sample size, study inclusion/exclusion criteria (including patient age, diagnosis, and certain comorbidities), measurements of baseline disease severity (e.g., number of comorbid physical or mental disorders, emergency room visits, or hospitalization before the index date), methods of economic evaluation, and funding sources. Additional information on study results was extracted with respect to measures of costs and outcomes as well as cost-effectiveness.

2.4. Analysis

The outcomes of interest included total healthcare costs, healthcare costs plus indirect costs, compliance with treatment, hospitalization rates, and change in clinical symptoms/or quality of life measurements. Results were compared and classified according to study designs, i.e., retrospective database analyses, conventional RCTs, and pragmatic RCTs plus naturalistic observational studies.

3. Results

The electronic search yielded 4417 studies but an initial review of titles led to the exclusion of 4220 because they did not focus on depression treatment, they were not comparative analyses of alternative antidepressants, or they did not include costs. For the remaining 197, the abstracts were reviewed to identify potentially relevant papers and a further 143 excluded mainly because on closer examination they were found not to be economic evaluations, or they were not based on a designated study design of this review. For the remaining 54, the full papers were reviewed and a further 17 excluded because they were not economic evaluations based on a database analyses, an RCT, or a naturalistic observational study. Reference lists of included papers and previous reviews were hand-searched and another three studies were identified, thus 40 papers were included in the final review: 28 retrospective database analyses and 12 prospective studies (six conventional RCTs, five pragmatic RCTs and one naturalistic observational study). A breakdown of inclusion and exclusion is given in the QUOROM diagram in Fig. 1.

In assessing the quality of economic evaluations of mental health interventions in a previous review, Evers et al. (1997) identified a number of common weaknesses in study design, including lack of randomization, short follow-up periods and unexplained sample sizes. In a more recent review of cost-effectiveness of treatments for depression, Barrett et al. (2005) highlighted specific difficulties in synthesizing evidence from various economic evaluations because of the use of different

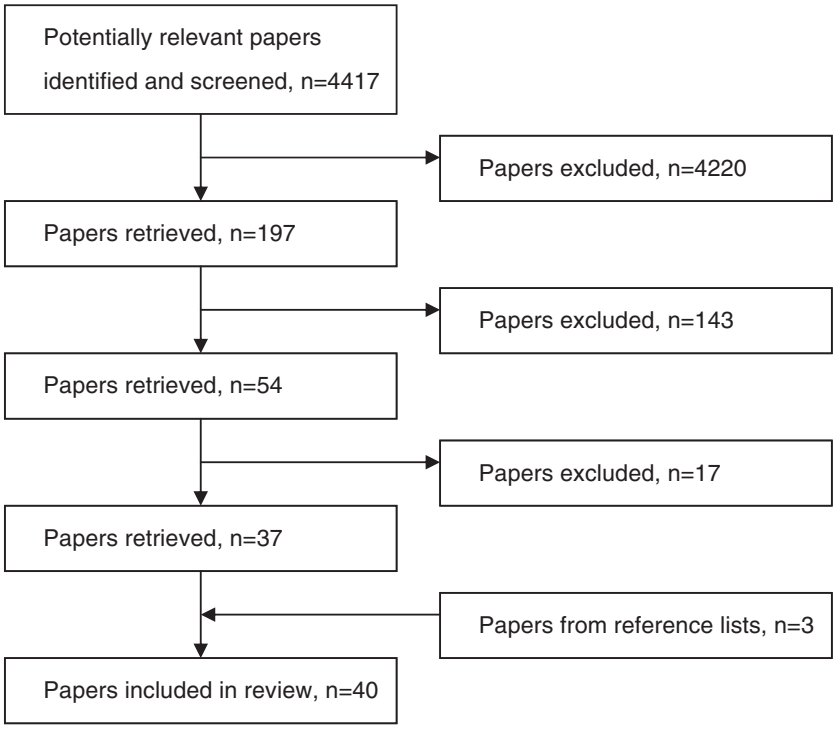

Fig. 1. QUOROM flow diagram of articles included in the systematic review.

Table 1
Characteristics of included papers of database analyses.

Study	Interventions	Country	Depression diagnoses	Cost perspective	Study period (months)	Outcomes	Economic evaluation	Sponsor
Wade et al. (2010) >=18 Y/O	Escitalopram (n=323), venlafaxine (n=215), generic SSRIs (n=1947)	UK	Severe depression according to GPRD	Health care	12	Hospitalizations per patient	Cost-consequences	H.Lundbeck A/S
Wu et al. (2009) >=18 Y/O	Escitalopram (n=10,465), SSRI/SNRIs (n=28,310)	USA	ICD-9-CM: 296.2, 296.3	Health care	6	Discontinuation, switching, time from discontinuation to the first ER visit	Cost-consequences	Forest Research Institute, Inc.
Tournier et al. (2009) >=66 Y/O	Citalopram (n=2321), fluoxetine (n=360), fluvoxamine (n=883), paroxetine (n=2353), sertraline (n=2269), nefazodone (n=360), trazodone (n=2342), venlafaxine (n=1937)	Canada	Not stated	Health care +out of pocket payments	12	Treatment non-persistence	Cost-consequences	Government
Wu et al. (2008a) >=65 Y/O	Escitalopram (n=459), SSRI/SNRIs (n=1517)	USA	ICD-9-CM: 296.2, 296.3	Health care	6	Discontinuation, switching rate, hospitalization rate	Cost-consequences	Forest Laboratories, Inc.
Wu et al. (2008b) >=65 Y/O	Escitalopram (n=459), citalopram (n=232)	USA	ICD-9-CM: 296.2, 296.3	Health care	6	Discontinuation, switching rate, hospitalization rate	Cost-consequences	Forest Laboratories, Inc.
Khandker et al. (2008) >=18 Y/O	Venlafaxine (n=5297), SSRIs (citalopram, fluoxetine, paroxetine, sertraline, n=43,653)	USA	ICD-9-CM 296.2, 296.3, 300.4, 311	Health care	12		Cost-analysis	Wyeth Research
Sheehan et al. (2008) >=18 Y/O	3 rd generation (n=83,800), 2nd generation (n=161,166), 1st generation ADs (n=21,699)	USA	ICD-9-CM 296.2, 296.3, 300.4, 311 300.01,300.21, 300.22, 300.23,300.3, 309.81, 308.3, 300.02, 300.00	Health care	6	Adherence rate, hospitalization rate	Cost-consequences	GlaxoSmithKline
Monfared et al. (2006) >=18 Y/O	Venlafaxine XR (n=3150), SSRIs (citalopram, fluoxetine, paroxetine, sertraline, n=13,994)	Canada	ICD-9-CM 296.2, 296.3, 300.4, 309.0, 309.1, 311	Health care +out of pocket payments	12	Treatment persistence, compliance rate	Cost-consequences	Wyeth Pharmaceuticals
Sheehan et al. (2005) >=18 Y/O	Paroxetine CR (n=10,072), sertraline (n=40,539), paroxetine (n=30,522), citalopram (n=29,722), fluoxetine (n=20,693), escitalopram (n=14,527)	USA	ICD-9-CM 296.2, 296.3, 300.4, 311 300.01,300.21, 300.22, 300.23,300.3, 309.81, 308.3, 300.02, 300.00, 293.89	Health care	6		Cost-analysis	None declared
Chung (2005) No age limitations	SSRIs (n=771), TCAs (n=171)[a]	USA	ICD-9 codes of 296, 300 (accompanied by CCC69), 309(accompanied by CCC72), and 311	Health care +out of pocket payments	[b]13.2		Cost-analysis	None declared
Sheehan et al. (2004) >=18 Y/O	Paroxetine CR (n=1275), paroxetine IR (n=2550)	USA	ICD-9-CM 296.2, 296.3, 300.4, 311 300.01,300.21	Health care	6	Time to discontinuation	Cost-consequences	GlaxoSmithKline
McLaughlin et al. (2004) >=18 Y/O	Citalopram (n=3175), sertraline (n=15,222)	USA	ICD-9-CM 296.2, 296.3, 300.4, 311	Health care	6	Treatment persistence, use of other ADs	Cost-consequences	Pfizer Inc.
Ackerman et al. (2002) No age limitations	TCAs (n=124 hospitalizations), MAOIs (n=9), atypicals (trazodone,	USA	ICD-9 296, 311	Health care (only hospital charges)	During hospitalizations		Cost-analysis	Government

	nefazodone, bupropion, n = 211), SSRIs (n = 798), venlafaxine (n = 119), multiple medications (n = 437)							
Optenberg et al. (2002) >= 18 Y/O	SSRIs (n = 697), TCAs (n = 311), no medications (n = 811)	USA	ICD-9-CM 296.2:	Health care	12	Hospitalization (%), inpatient days	Cost-consequences	GlaxoSmithKline
Wan et al. (2002a) >= 18 Y/O	Venlafaxine (including venlafaxine XR, n = 468), SSRIs (n = 8625)	USA	ICD-9-CM 296.2, 296.3, 300.4, 309.0, 309.1, 311	Health care + out of pocket payments	6	Adherence, odds of hospitalization	Cost-consequences	Wyeth-Ayerst Research
Wan et al. (2002b) >= 18 Y/O	Venlafaxine (including venlafaxine XR, n = 353), SSRIs (n = 7330)	USA	ICD-9-CM 296.2, 296.3, 300.4, 309.0, 309.1, 311	Health care + out of pocket payments	6	Adherence	Cost-consequences	Wyeth-Ayerst Research
Polsky et al. (2002) 18–64 Y/O	Fluoxetine (n = 840), sertraline (n = 386), paroxetine (n = 545)	USA	ICD-9-CM 296.2, 296.3	Health care	12	Treatment persistence	Cost-consequences	SmithKline Beecham
Crown et al. (2001) >= 18 Y/O	Fluoxetine (n = 882), paroxetine (n = 352), sertraline (n = 796)	USA	ICD-9-CM 296.2, 296.3, 300.4, 309.0, 309.1, 311	Health care	24	Guideline adherence	Cost-consequences	Eli Lilly and Company
Baker et al. (2001) No age limitations	SSRIs (n = 2877), TCAs (n = 2303), atypical/heterocyclic agents (n = 447)	USA	ICD-9: 296.2, 296.3, 300.4, 311	Health care + out of pocket payments	12	Guideline adherence (treatment persistence)	Cost-consequences	Pfizer Inc.
Poret et al. (2001) >= 18 Y/O	Bupropion SR (n = 115), fluoxetine (n = 564), paroxetine (n = 393), sertraline (n = 481), venlafaxine (n = 73), TCAs (n = 145)	USA	ICD-9-CM 296.2, 296.3, 300.4, 309.0, 309.1, 311	Health care	6		Cost-analysis	None declared
Sullivan et al. (2000) >= 19 Y/O	Venlafaxine (n = 208), SSRIs (n = 332), TCAs (n = 191), other ADs (n = 250)	USA	ICD-9-CM 296.20-26, 296.30-36, 296.50-296.56, 300.4, 300.9, 296.90, 311.0	Health care	12		Cost-analysis	Wyeth-Ayerst Laboratories
Croghan et al. (2000) 18-64 Y/O	Fluoxetine (n = 1351), sertraline (n = 508), TCAs (n = 698)	USA	ICD-9-CM 296.2, 296.3, 300.4, 309.1, 311	Health care	12	Hospitalization	Cost-consequences	Eli Lilly and Company
Berndt et al. (2000) 18-65 Y/O	Fluoxetine (n = 945), paroxetine (n = 492), sertraline (n = 905)	USA	ICD-9 296.2, 296.3, 300.4, 311.0	Health care + out of pocket payments	12	Hospitalization	Cost-consequences	Pfizer Inc.
Dobrez et al. (2000) 18–64 Y/O	SSRIs (n = 1982), TCAs (n = 696)	USA	ICD-9-CM 296.2, 296.3, 300.4, 309.0, 309.1, 311	Health care	12	Treatment persistence	Cost-consequences	Eli Lilly and Company
Griffiths et al. (1999) >= 19 Y/O	Venlafaxine (n = 188), TCAs (n = 172)	USA	ICD-9-CM 296.20-26, 296.30-36, 296.50-296.56, 300.4, 309.0, 296.90, 311.0	Health care	12		Cost-analysis	Wyeth-Ayerst Laboratories
McCombs et al. (1999) 18-100 Y/O	TCAs (n = 970), heterocyclics (n = 311), paroxetine (n = 97), sertraline (n = 130), fluoxetine (n = 140)	USA	ICD-9 296.2, 296.3	Health care	12	Guideline adherence	Cost-consequences	Eli Lilly and Company
Sclar et al. (1999) 18–65 Y/O	TCA(amitriptyline, n = 237), citalopram (n = 71), fluoxetine (n = 411), paroxetine (n = 334), sertraline (n = 286)	USA	ICD-9-CM 296.2:	Health care + out of pocket payments	6	Treatment persistence	Cost-consequences	Forest Laboratories, Inc. and Parke-Davis division of Warner-Lambert Company
Russell et al. (1999) 18–65 Y/O	Sertraline (n = 905), paroxetine (n = 492), fluoxetine (n = 945)	USA	ICD-9 296.2, 296.3, 300.4, 311.0	Health care	12	Treatment persistence	Cost-consequences	Pfizer Inc.

ADs: antidepressants.

[a] Only a subsample with depression is reported here.

[b] The average length of the post-baseline period for each individual.

outcome scales and different study perspectives across studies. The key characteristics of the included papers are summarized in Tables 1 and 2. Follow-up periods of five included RCTs were less than or equal to 24 weeks. Fifteen studies lasted for 6 months and the remaining 19 studies for at least 12 months. The effectiveness of the treatments was recorded using nearly 20 different outcome measures. Only four studies used a primary outcome measure of quality of life. While indirect costs including productivity losses may occur as a result of impaired working ability, only 16 papers considered a broad perspective of costs and the remainder (n = 24) solely considered costs to healthcare systems. Two of the included studies were carried out in multinational settings; another eight studies were from European countries, one from India, and the remainder (n = 29) from North America (Tables 1 and 2).

3.1. Findings from retrospective database analyses

3.1.1. Characteristics and methodological approaches of the included studies based on database analyses

All included database analyses were carried out in the United States/Canada with one exception using primary care data from the United Kingdom (Wade et al., 2010) (Table 1). The study populations were mostly adults aged 18 years or above (some of them recruited only working-age adults), with the exception of three studies focusing on elderly populations (Tournier et al., 2009; Wu et al., 2008a,b). The majority of these analyses adopted a similar methodology, based on the identification of patients who had a paid insurance claim that indicated a diagnosis of a depressive disorder and treatment with antidepressants. Diagnoses of a depressive disorder included major depressive disorder and dysthymic disorder (or neurotic depression) in most studies; several studies recruited only subjects with major depressive disorder and one study researched exclusively on subjects with severe depression (Wade et al., 2010). Another three studies recruited subjects with a diagnosis of either depression or anxiety disorder (Sheehan et al., 2004, 2005, 2008) while the others also included subjects with a diagnosis of bipolar depression (Griffiths et al., 1999; Sullivan et al., 2000) or bipolar disorder (Ackerman et al., 2002) (Table 1). In most cases, an intention-to-treat (ITT) principle was applied and patients were assigned to a drug cohort on the basis of their initial prescription, with resource utilization data over a specified study period after the first prescription analyzed and compared between drug cohorts. The most often used proxies for disease severity was baseline healthcare utilization and number of concomitant disease states; number of emergency room visits or hospitalizations before index date, or severity subcodes of diagnoses were also used.

A healthcare perspective on costs was adopted in all studies, although some of them also took into consideration out-of-pocket payments by patients including copayment, coinsurance, and/or deductibles (Table 1). Among the 28 database studies, seven were cost analyses, and the remaining 21 were cost-consequence analyses where costs were reported alongside a range of outcome measures. Treatment persistence, odds of hospitalization, and guideline adherence were the most frequently used outcome measures. Study periods ranged from 6 to 24 months. In the 28 included studies, 23 were funded by pharmaceutical companies. In one of the two studies funded by government agencies (Ackerman et al., 2002; Tournier et al., 2009), the authors provided consultancy services to the pharmaceutical industry (Tournier et al., 2009). In the further two studies in which funding sources were not stated, the authors either provided consultancy services to the pharmaceutical industry (Sheehan et al., 2005) or were employees of the pharmaceutical companies (Poret et al., 2001). Only one study declared no conflicts of interest (Chung, 2005) (Table 1).

3.1.2. Economic evaluations comparing antidepressants using database designs

Four studies were primarily designed to compare escitalopram with other antidepressants. Escitalopram was shown to have better treatment persistence and lower total healthcare costs compared to other SSRI/SNRIs both in a larger sample of adult patients (Wu et al., 2009) and in a smaller sample of geriatric patients (Wu et al., 2008a). In another study with severely depressed adult patients, there were significantly fewer hospitalizations per patient in the escitalopram versus venlafaxine or generic SSRI groups; the total annual healthcare expenditure per patient was lower in the escitalopram group compared to venlafaxine but similar with escitalopram and generic SSRIs (Wade et al., 2010). Escitalopram was shown to have better treatment persistence, a lower hospitalization rate, and lower total healthcare costs than citalopram in a geriatric population (Wu et al., 2008b). As above studies were funded by the same pharmaceutical companies and escitalopram was the antidepressant of interest in all of them, findings from a cost analysis primarily designed to compare another antidepressant (paroxetine controlled release (CR)) with other SSRIs (including escitalopram) were provided: the average unadjusted 6-month medical costs of escitalopram treatment (n = 14,527) were slightly lower than the average costs of SSRIs as a whole (n = 136,003) in the treatment of depressed patients, but the costs of escitalopram users were higher than the average costs of those prescribed SSRIs when treating patients with anxiety disorder or depression comorbid with anxiety disorder (Sheehan et al., 2005).

While comparing venlafaxine with SSRIs (citalopram, fluoxetine, paroxetine, and sertraline), better treatment persistence was found for venlafaxine XR but total direct medical costs were comparable with venlafaxine and SSRIs (Monfared et al., 2006). Patients prescribed with venlafaxine were reported to have lower odds of hospitalization for non-mental-health reasons than those with SSRIs, while total healthcare costs were similar between the two groups; these studies failed to demonstrate differences in treatment persistence between venlafaxine XR and SSRIs (Wan et al., 2002a,b). Two cost analyses with similar study designs revealed that total medical expenditures were generally similar among patients receiving venlafaxine, SSRIs, or TCAs as a second-line therapy for depression (Griffiths et al., 1999; Sullivan et al., 2000). Another study comparing healthcare costs of patients who switched antidepressants versus those who did not found that switchers had higher total healthcare costs than non-switchers. For patients switching from an SSRI to venlafaxine, mean medical cost reductions offset higher pharmacy costs of venlafaxine after the switch, and for those switching from venlafaxine to an SSRI, mean medical and pharmacy costs declined after the switch (Khandker et al., 2008). As each of the above studies was funded by the same pharmaceutical

company, findings from another study funded by a government agency are informative (Tournier et al., 2009). This showed similar treatment persistence and costs for medical service utilization and psychiatric hospitalization between venlafaxine (n = 1937) and SSRIs (n = 8186).

There were 12 included database analyses that used TCAs as a comparator treatment. One study showed that patients treated with SSRIs were more likely to meet treatment duration recommendations than those treated with TCAs; and among compliant patients, mean total healthcare costs were lower for SSRIs (Baker et al., 2001). SSRIs were shown in a bivariate probit model to reduce patients discontinuing pharmacotherapy compared to TCAs, but total healthcare charges were similar between the two groups (Dobrez et al., 2000). Despite comparable total healthcare expenditures between treatment groups, SSRI users were shown to have higher depression-related service expenditures but have lower non-depression-related service expenditures than TCA users (Sullivan et al., 2000). It was further revealed by Baker et al. (Baker et al., 2001) that among patients compliant with treatment duration recommendations, non-depression-related costs were lower for those prescribed SSRIs than for those prescribed TCAs (Baker et al., 2001). SSRIs probably reduced overall outpatient visits and the use of other prescription drugs, but increased utilization of services for depression, which then canceled out the potential cost advantage of SSRIs over TCAs (Chung, 2005).

Compared to patients prescribed TCAs, fluoxetine patients were shown to be half as likely to be hospitalized (Croghan et al., 2000) and have lower total healthcare costs (McCombs et al., 1999). Similarly, citalopram was reported to have better treatment persistence and lower total healthcare costs than the TCA amitriptyline (Sclar et al., 1999). Lower nursing home and other costs were found in a comparison of sertraline versus TCAs (McCombs et al., 1999), but another study revealed similar likelihood of hospitalization for patients initially prescribed sertraline and TCAs (Croghan et al., 2000). In a study comparing bupropion SR with other antidepressants, total healthcare costs were shown to be lower for patients treated with bupropion SR than for those treated with TCAs and in comparison with bupropion SR, patients initiating therapy with sertraline had significantly higher mental health payments (Poret et al., 2001).

Turning to comparisons between different SSRIs, the comparative results were largely mixed. A head-to-head comparison favored sertraline in having lower depression-related costs than citalopram (McLaughlin et al., 2004), but a contradictory finding emerged in another study favoring citalopram in having lower total and depression-related healthcare costs (Sclar et al., 1999). Likewise, sertraline was shown to have lower total and depression-related costs than fluoxetine in one study (Berndt et al., 2000), but in another study, fluoxetine was shown to have better treatment persistence than sertraline and paroxetine while total healthcare costs were similar between antidepressant groups (Polsky et al., 2002). In another two studies, no significant differences were noted among patients treated with fluoxetine, paroxetine, and sertraline.in depression-related costs (Russell et al., 1999) or total healthcare costs (Crown et al., 2001). In the only study examining the cost-persistence ratio (with non-persistence defined as treatment duration of less than 180 days), paroxetine was shown to have the most favorable cost-persistence ratio, but fluoxetine was considered the best choice in terms of incremental cost-persistence ratio (the difference in costs between the two treatments divided by the difference in outcomes (frequency of persistent treatments) between the two treatments) (Tournier et al., 2009).

Beyond comparisons between different antidepressants, one study with patients of major depressive disorder revealed significantly higher total healthcare costs for patients not receiving any initial psychotropic medications compared to either those treated with TCAs or SSRIs (Optenberg et al., 2002). Further studies compared the same antidepressant compounds with different release patterns. Paroxetine CR was shown to have better treatment persistence and lower medical costs relative to paroxetine immediate release (IR) (Sheehan et al., 2004); compared to other SSRIs (including paroxetine IR) as a group, paroxetine CR was also shown to have lower medical costs (Sheehan et al., 2005). Several included studies principally focused on hospital charges (Ackerman et al., 2002; Croghan et al., 2000). In one of them, initial use of heterocyclic agents was shown to be associated with higher hospital charges than monoamine oxidase inhibitors (MAOIs), SSRIs and venlafaxine, despite the major cost drivers being other more expensive procedures, e.g., electro-convulsive therapy, rather than choices of antidepressant treatments (Ackerman et al., 2002). The remaining study defined all antidepressants launched after 2002 as "third-generation antidepressants" (bupropion XL, duloxetine, venlafaxine XR, escitalopram, paroxetine CR) and reported that newer generation antidepressants were associated with lower total medical costs (excluding pharmacy costs), lower odds of all-cause hospitalization, and better adherence (Sheehan et al., 2008).

3.2. Findings from economic evaluations comparing antidepressants using prospective study designs

3.2.1. Conventional RCTs

For illustrative purposes, findings from conventional RCTs were also reviewed. Four of the six included conventional RCTs were head-to-head cost-effectiveness comparisons between antidepressant treatments for patients with major depressive disorder: three studies compared the cost-effectiveness of escitalopram to duloxetine (aged 18–65) (Wade et al., 2008), citalopram (aged 18–65) (Fantino et al., 2007), and venlafaxine (aged 18–85) (Fernandez et al., 2005), respectively. The results revealed that escitalopram appeared as a dominant strategy compared to either duloxetine or citalopram; it had similar effectiveness but lower costs compared with venlafaxine. The other head-to-head comparison examined the cost-effectiveness of mirtazapine versus paroxetine and suggested that mirtazapine may be a more cost-effective treatment choice (Romeo et al., 2004).

In the remaining conventional RCTs, fluoxetine was compared to placebo or psychological treatment for the management of common mental disorders in adults (Patel et al., 2003) and major depressive disorder in adolescents (Domino et al., 2008). Fluoxetine was shown to be more cost-effective than placebo and psychological treatment over both the short term (2 months) and long term (12 months) in the former study (Patel et al., 2003) and in the latter one, fluoxetine was more

Table 2
Characteristics of included papers of prospective studies.

Study	Interventions	Country	Cost perspective	Duration of costs/ outcomes	Primary outcome	Economic evaluation	Main results	Sponsor
Conventional RCTs								
Wade et al. (2008) 18–65 Y/O	Escitalopram (n = 141), duloxetine (n = 146)	Multisite	Society (healthcare + loss of productivity)	24 weeks	Change in Sheehan Disability Scale (SDS) score	Cost-effectiveness	Escitalopram was more effective on the SDS score and less costly compared to duloxetine.	H. Lundbeck A/S
Domino et al. (2008) 12–18 Y/O	Fluoxetine (n = 94), CBT (n = 89), fluoxetine + CBT (n = 92), placebo (n = 94)	USA	Society (healthcare + family costs)	12 weeks	Change in Children's Depression Rating Scale-Revised	Cost-effectiveness	Fluoxetine was more cost-effective than placebo treatment if the threshold of $100,000 per QALY was applied	Government
Fantino et al. (2007) 18–65 Y/O	Escitalopram (n = 138), citalopram (n = 142)	France	Society (healthcare + loss of productivity), health care	8 weeks	Remission, Montgomery-Asberg Depression Rating Scales Self-reported (MADRS-S)	Cost-effectiveness	Escitalopram probably had better effectiveness (both remission and MADRS-S) and a lower cost than citalopram.	H. Lundbeck A/S
Fernandez et al. (2005) 18–85 Y/O	Escitalopram (n = 126), venlafaxine (n = 125)	Multisite	Health care (with society perspective considered in a sensitivity analysis)	8 weeks	EQ5D	Cost-effectiveness	Healthcare costs were lower for escitalopram compared with venlafaxine. No between-group difference in EuroQoL was noted.	H. Lundbeck A/S
Romeo et al. (2004) No age limitations	Mirtazapine (n = 93), paroxetine (n = 84)	UK	Society (healthcare + loss of productivity), health care	24 weeks	17-HAMD	Cost-effectiveness	Mirtazapine was probably a cost-effective treatment choice compared to paroxetine according to CEAC.	Organon Laboratories
Patel et al. (2003) >= 17 Y/O	Fluoxetine (n = 150), placebo (n = 150), psychological treatment (n = 150)	India	Health care + patient/family costs	12 months	Psychiatric morbidity (Revised Clinical Interview Schedule: CISR total score)	Cost-effectiveness	Fluoxetine was more cost-effective than placebo in the short term and long term.	Charitable foundation
Pragmatic RCTs								
Serrano-Blanco et al. (2009) 18–65 Y/O	Fluoxetine (n = 53), imipramine (n = 50)	Spain	Society (healthcare + loss of productivity)	6 months	EuroQoL-5D	Cost-utility	Imipramine dominated fluoxetine with 81.5% of the bootstrap replications in the dominance quadrant.	Government

Serrano-Blanco et al. (2006a) 18–65 Y/O	Fluoxetine (n = 53), imipramine (n = 50)	Spain	Society (healthcare + loss of productivity)	6 months	Montgomery-Asberg Depression Rating Scales (MADRS)	Cost-effectiveness	The imipramine group had fewer treatment-associated costs than fluoxetine when effectiveness was similar between treatment groups.	Government
Peveler et al. (2005) >= 18 Y/O	TCAs (n = 111), SSRIs (n = 109), Lofepramine (n = 104)	UK	Health care	12 months	Depression-free weeks	Cost-effectiveness	CEAC suggested that SSRIs were likely to be the most cost-effective option although the probability of this did not rise above 0.6.	Government
Hosak et al. (2000) No age limitations	Amitriptyline(n = 31), citalopram(n = 29), fluoxetine(n = 30)	Czech Republic	Health care	6 months	Hospitalization-free days	Cost-effectiveness	Neither cost nor effectiveness was significantly different among the treatment groups.	None declared
Simon et al. (1999) No age limitations	Desipramine (n = 135), fluoxetine (n = 128), imipramine (n = 130)	USA	Health care	24 months	Remission, HDRS, SCL, SF-36	Cost-consequences	The fluoxetine group did not differ from TCA groups on any measure of depression severity or quality of life; total medical costs were essentially identical between groups.	Lilly Research Laboratories
Naturalistic observational study								
Serrano-Blanco et al. (2006b) 18–75 Y/O	Fluoxetine(n = 100), paroxetine (n = 110), citalopram(n = 38), sertraline(n = 53)	Spain	Society (healthcare + loss of productivity)	6 months	EQ5D	Cost-utility	Fluoxetine dominated paroxetine and citalopram with 63.4% and 79.3% of the bootstrap replications in the dominance quadrant, respectively; fluoxetine was cost-effective over sertraline with 83.4% of the bootstrap replications below the threshold of 33,936 US$/QALY.	Government

cost-effective than placebo treatment when the threshold of $100,000 per QALY (the quality-adjusted life year) was applied (Domino et al., 2008).

Except for one study adopting a healthcare payer perspective with a societal perspective considered in a sensitivity analysis (Fernandez et al., 2005), all the conventional RCTs estimated costs from a broader societal perspective, either healthcare with loss of productivity costs (Fantino et al., 2007; Romeo et al., 2004; Wade et al., 2008) or healthcare with patient and/or family costs (Domino et al., 2008; Patel et al., 2003). The outcome measures used in these conventional RCTs included the Sheehan Disability Scale score (SDS), Children's Depression Rating Scale-Revised, Montgomery-Asberg Depression Rating Scales Self-reported (MADRS-S), EQ-5D, 17-item Hamilton Depression Rating Scale (HDRS-17), remission, and psychiatric morbidity rated by the Clinical Interview Schedule, Revised (CISR total score). Study periods ranged from 8 to 24 weeks, with the exception of Patel et al. (Patel et al., 2003) who measured and compared cost-effectiveness up to 12 months (Table 2).

3.2.2. Pragmatic RCTs and naturalistic observational studies

Compared to conventional RCTs, pragmatic RCTs aim to inform decisions about clinical practice by testing effectiveness with relatively unselected participants and under flexible conditions. There were five pragmatic RCTs and one naturalistic observational study included in this review (Table 2). From a societal perspective, imipramine (a TCA) was shown to be a more cost-effective treatment than fluoxetine in a 6-month randomized prospective naturalistic study as the similar effectiveness was counteracted by lower total costs for the imipramine group (Serrano-Blanco et al., 2006a). Imipramine was also found to dominate fluoxetine in a cost-utility analysis (Serrano-Blanco et al., 2009).

The remaining three pragmatic RCTs adopted a healthcare payer perspective. One of them compared TCAs, SSRIs and the modified TCA lofepramine as first choice of treatment for depressive disorder in primary care, and revealed no significant differences between the antidepressants in either outcomes or costs during the 12 months of follow up; however, the cost-effectiveness acceptability curves suggested that SSRIs were likely to be the most cost-effective option despite the probability of this not rising above 0.6 (Peveler et al., 2005). In a sample of depressive patients in primary care, randomization to fluoxetine or a TCA (desipramine or imipramine) led to similar clinical outcomes and overall treatment costs for 24 months (Simon et al., 1999). Using the number of hospitalization-free days as the effectiveness measure, one pragmatic RCT compared groups of initial use of antidepressants (amitriptyline, citalopram, and fluoxetine) and revealed no differences in either depression treatment costs or effectiveness over the period of 6 months (Hosak et al., 2000).

From a societal perspective, the only non-randomized prospective 6-month follow-up naturalistic study showed that fluoxetine dominated paroxetine and citalopram in cost-effectiveness and had a high probability of being more cost-effective than sertraline (Serrano-Blanco et al., 2006b). Overall, half of the included pragmatic RCTs and the naturalistic observational study adopted the healthcare payer perspective while the others estimated costs from a broader societal perspective. The outcome measures in these studies included the EQ-5D, MADRS, depression-free weeks, hospitalization-free days, HDRS score, the Medical Outcomes Study SF-36 Health Survey (SF-36), the anxiety and depression subscales of the Hopkins Symptom Checklist (SCL), and remission. The study periods ranged from 6 to 24 months (Table 2).

4. Discussion

4.1. Summary of main results comparing database analyses and prospective studies

Based on the available evidence from both database analyses and conventional RCTs, depressed patients prescribed escitalopram had lower total healthcare costs than those prescribed certain SSRIs, and escitalopram appeared more effective than certain SSRIs in terms of treatment persistence and some clinical symptom measures. Compared to venlafaxine, patients prescribed escitalopram in some studies had lower total healthcare costs. The validity of applying these results to depressed patients with anxiety disorder has not yet been established.

In database analyses, patients using TCAs generally had comparable healthcare costs to those using SSRIs, while in some studies, higher non-depression related costs and lower depression related costs were found in TCA users. Some other database studies reported that SSRI users had greater treatment persistence and lower total healthcare costs than TCA users. Different results emerged from prospective studies. From a healthcare payer perspective, patients prescribed TCAs were shown to have comparable costs and clinical outcomes with SSRI users in pragmatic RCTs (Hosak et al., 2000; Peveler et al., 2005; Simon et al., 1999). However, from a societal perspective, TCA users in pragmatic RCTs, had similar or even better outcomes but lower total costs than SSRI users (Serrano-Blanco et al., 2006a; Serrano-Blanco et al., 2009).

Without randomization, the above results comparing TCAs with SSRIs in database analyses may reflect physician choice based on heterogeneous presentations of depressed patients that could not be captured by the demographic factors or proxy variables for disease severity used in the included studies. The findings that TCA users had higher non-depression-related costs and lower depression-related costs than SSRI users also implied that in real-world settings, patients prescribed TCAs are probably different from SSRI users in terms of clinical features of depression or comorbid physical illnesses. Once randomization was applied in a pragmatic RCT, TCA users were shown to have equal or better effectiveness than SSRI users; total related costs were found to be equal or even lower for patients prescribed TCAs. It is also worth noting that the cost-effectiveness advantage of TCAs over SSRIs revealed in the pragmatic RCTs (but not in the database analyses) may not be driven by the lower drug acquisition costs of TCAs considering that the wider cost perspective, i.e., societal perspective, in the pragmatic RCTs would mean the contribution of drug acquisition costs to total costs is very low. Therefore, the cost-effectiveness differentials between TCAs and SSRIs among these studies could be driven by other factors that warrant further research.

4.2. Strengths and limitations of economic evaluations using database analyses

Database analyses can supplement RCTs to inform decision-making in actual clinical practice, as conventional RCTs may not

accurately reflect the real-world cost-effectiveness of competing antidepressant treatments (Crown, 2000). Appropriate allocation of scarce resources among competing choices is a fundamental policy concern. Economic evaluations conducted within the context of conventional RCTs may not be sufficient to inform decision-making, considering that individual behavior in conventional RCTs is controlled through a strict, protocol-driven environment. In light of these considerations, more flexible study designs are employed in pragmatic RCTs to measure cost-effectiveness in a situation closer to the real-world settings. However, the randomization procedure makes physician choice and other important factors influencing initial choice of antidepressant treatment in real-world settings unobservable.

Economic evaluations based on RCTs may be underpowered. The sample size of an RCT is usually calculated according to clinical rather than economic criteria, and a much larger sample may be needed to determine the significance of economic outcomes (Briggs, 2000). Although modeling and other methods have been widely used in recent economic evaluations, these approaches rely heavily on assumptions that may not be easily testable. By contrast, retrospective database analyses using routine administrative data can offer quick access to large samples of patients in naturalistic settings. Besides the advantages of lower research costs and larger sample size than RCTs, database analyses potentially assess economic outcomes over longer periods of follow-up and from more heterogeneous populations, and hence are capable of supplementing RCTs to inform decision-making.

Despite these strengths, several limitations should be borne in mind when interpreting results from database analyses. Lack of clinical data on effectiveness is clearly a major limitation. Many database analyses in this review focus on comparisons of costs. Among studies comparing costs and outcomes simultaneously, persistence of treatment and rate of hospitalization are frequently used as proxies for clinical effectiveness. There are concerns regarding the use of these proxies; for example, poor outcome tends to be assumed for individuals who discontinue their index antidepressants without taking into consideration fast responders or patients with milder disease severity. The use of hospitalization rate as an effectiveness index may be problematic as it is also a resource measure (and hence potentially included in the measurement of cost). Efforts to improve the effectiveness measurements have been noted in the literature, such as the application of a new approach to estimate health values (as an effectiveness index) of alternative treatment patterns based on expert panels (Watkins et al., 2009). Further efforts should be made to incorporate newer approaches to effectiveness measurement with administrative database analyses.

Compared to the more recent RCTs, database analyses usually adopt a narrower definition of costs, and which may not therefore pick up the impact of treatment on loss of productivity and employment that may actually contribute substantially to the overall costs of depression (Thomas and Morris, 2003; Wang et al., 2003).

There are biases to be considered in database analyses. Confounding or selection bias due to nonrandomized study design is clearly important. For example, a patient's medical and social history, disease severity, and a physician's characteristics may influence both the initial choice of antidepressant and the subsequent outcome. To address this heterogeneity issue, strategies including matching (Sheehan et al., 2004) and the use of propensity score techniques (Wade et al., 2010) were noted. Furthermore, the reverse causality of medical care utilization to drug choice can be minimized through defining the drug choice at baseline and estimating utilization during the following period. While this limits potential inquiries to compare treatment effects in a counterfactual scenario using database analyses, it also is cognizant of the real-world situations in which physician preferences and heterogeneity of clinical presentations influence both antidepressant choice and cost-effectiveness outcomes for a patient with depression.

Publication/sponsorship bias would be another major concern as complex statistical analyses could leave the results open to a degree of subjectivity. Since 23 out of the total 28 database analyses included in this review were sponsored by the pharmaceutical industry and another three studies had authors affiliated with pharmaceutical companies, the potential for overestimation of effect due to sponsorship should be kept in mind, especially when no company has apparently published data that indicate their compound to be less cost-effective than a rival. Of course, this consideration applies to many randomized trials too.

In this review, the antidepressant of interest was usually new or just available in the months leading up to the study, while the comparator drugs were mostly well established and continuously available. Many physicians might not be able to prescribe newer antidepressants in the beginning of the study period and might have had inadequate time to gain sufficient experience with them. Some of them might preferentially prescribe newer antidepressants to those patients refractory to previous treatment, a tendency that has been called channeling or allocation bias (Egberts et al., 1997). However, the reverse might also be true, if not more common, i.e., to prescribe newer antidepressants to patients with milder disease to gain more clinical experience while the perceived mild side effects would not harm patients. For example, patients who are able to work may be prescribed newer agents because these drugs are perceived as less disruptive and more tolerable. The timing of studies therefore might affect the economic outcomes presented due to the different intervals from the launch dates of competing antidepressants.

Furthermore, diagnostic heterogeneity in the studied populations was noted (please see Table 1). These population characteristics may act as confounds when looking at the relative cost-effectiveness of the various antidepressants.

Although most of the included database analyses adopt an intention-to-treat (ITT) design, this approach may not be directly transferrable from the analysis of RCTs where it was originally used. The most important aim of ITT is to maintain treatment groups that are similar apart from random variation. In database analyses, patients are of course not randomized to treatments and the possibility for selection bias must be addressed by statistical methods other than ITT analysis. Furthermore, the second fundamental idea behind ITT is to reduce bias that might be introduced by excluding patients who did not complete the originally assigned course of therapy from the analyses (Gillings and Koch, 1991). Yet, most database analyses excluded those not continuously enrolled in the insurance program during the study period, hence bringing in bias.

Except for one study from the United Kingdom (Wade et al., 2010), all the database analyses are from the United States/Canada and so all studies are from developed countries.

Generalizability of effectiveness and cost data across different countries might not be straightforward. Not only do prescribing costs differ dramatically between settings, but also healthcare systems are organized in very different ways, particularly when looking at low- and middle-income countries (Dixon et al., 2006; Knapp et al., 2006). Moreover, many of the included studies are based on private insurance databases in which the subjects might be healthier, with different socioeconomic characteristics, or provided with different antidepressant choices compared to people with public or no insurance (Chung, 2005; McCombs et al., 1999). Future research is needed from developing countries and covering different insurance systems, as well as a wider range of populations.

Cost-effectiveness data for populations with different characteristics/comorbidity are not available. Despite studies comparing the characteristics across subjects initially treated with individual antidepressants, there have been no cost-effectiveness comparisons of individual antidepressant treatments across specific populations with different needs.

5. Clinical implications

This review suggests database analyses are an important source of evidence on the potential cost-effectiveness of alternative antidepressant treatments. Even though database analyses are susceptible to bias and confounding, they have the advantage of being based on observations from real-world practice. Given the limited external validity of RCTs, database analyses using data from actual clinical practice can usefully contribute to our understanding of the economic outcomes of alternative antidepressant treatments. Prospective and retrospective studies have their own strengths and limitations. It is essential to assess economic outcomes across a broad range of contexts using a range of study designs, and only findings that are consistent across a number of study designs and healthcare settings should be accepted with confidence.

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Conflict of interest

MK has acted as consultant and speaker for Lundbeck and Bristol Myers Squibb. PM has received speaker and consultancy fees from Lundbeck, Bristol Myers Squib, Lilly and Janssen-Cilag. YP declares no conflicts of interest.

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Treatment costs for depression with pain and cardiovascular comorbidities

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ABSTRACT

Objective: As depressive disorders are highly heterogeneous, and as patients exhibit wide differences in clinical characteristics and comorbidities, we aim to examine whether and how demographic and clinical correlates affect healthcare costs for patients with depression in a real-world setting.
Method: A national cohort of adult patients (n = 216,557) who received treatment for depression was identified from the National Health Insurance Research Database in Taiwan. Factors associated with service use and healthcare costs over a 12-month period were explored, with a particular focus on past treatment history, comorbid physical illnesses, painful physical symptoms, and choice of initial antidepressants.
Results: Depression severity, past treatment history, comorbid mental/physical illnesses, painful physical symptoms, and choice of initial antidepressants were found to be associated with healthcare costs in the following year, although the nature of the associations differed across cost categories. The presence of comorbid cardiovascular disease or certain painful physical symptoms at baseline was associated not only with higher non-psychiatric but also with higher psychiatric costs; moreover, patients with these comorbidities were shown to have increased use of psychiatric emergency and inpatient services.
Conclusion: Healthcare costs for depression are affected by a number of clinical characteristics and comorbidities of patients. The importance of comorbid pain and cardiovascular conditions warrants further research.

1. Introduction

Unipolar depressive disorder was the fourth leading cause of disease burden among all diseases in 2002 (Mathers and Loncar, 2006) and is predicted to become the leading cause in 2015 (WHO, 2008). The total direct healthcare costs of depression in Taiwan, as in many other countries, rose by 50% over the period of 2000–2002 (Chan et al., 2006); the prevalence of antidepressant use also doubled from 1997 to 2004 (Chien et al., 2007). This could imply an increase in the need for depression treatment, a reduction in the treatment gap, or over-provision of care. Given the anticipated rise in the future healthcare costs for patients with depression, it would help inform decision-making to assess the impact of depression treatment from an economic perspective.

Depressive disorders comprise a group of heterogeneous conditions. The extent to which treatment history, comorbidities of physical/mental illnesses, and choice of antidepressants can influence healthcare costs remains to be determined. Depression is known to be associated with a variety of physical conditions (Katon, 2003) of whom cardiovascular diseases (CVD) and painful physical symptoms (PPS) warrant further investigation. Depression and CVD are projected to be the first and second leading causes of health-related burden in 2015 (WHO, 2008), and there is accumulating evidence suggesting close interrelationships between these highly-prevalent conditions (Sorensenf et al., 2005; Thombs et al., 2006): for instance, depressive symptoms have been found to be a risk factor for cardiac events in patients with coronary heart disease (Barth et al., 2004; van Melle et al., 2004). To assess the economic impact of treatment for depression, PPS should also be carefully considered. Previous studies have revealed high prevalence of pain complaints in depressed patients (Bair et al., 2003; Husain et al., 2007; Ohayon and Schatzberg, 2003) and outcomes of treatment for depression may be poorer in the presence of PPS (Fava et al., 2004; Gameroff and Olfson, 2006; Leuchter et al., 2010).

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Furthermore, individual antidepressants have been shown to have a wide range of cardiovascular effects (Taylor, 2008), and antidepressants may differ in the effectiveness for the relief of PPS. Therefore, the presence of these co-occurring CVD and PPS may influence the choice of antidepressants and healthcare utilization, with potential impact on healthcare costs.

The current study, conducted in a real-world setting, seeks to measure healthcare costs for people with depression using claims data from the National Health Insurance Research Database (NHIRD) in Taiwan. The objective of this study is to identify which demographic and clinical characteristics and comorbidities are associated with total healthcare costs, as well as costs for specific groups of services, with a particular focus on comorbid pain and cardiovascular diseases.

2. Materials and methods

2.1. Data

Taiwan is a country with a population of around 23,000,000. The GDP per capita in 2003/2004 was 13,773/15,012 US dollars. National Health Insurance (NHI) in Taiwan is a single-payer compulsory social insurance plan that centralizes the disbursement of healthcare funds and guarantees equal access to healthcare for all citizens. In 2003, there were 21,869,478 individuals enrolled in the NHI with a coverage rate of 96%. The NHI contracted 17,022 medical institutions, which constituted 93.8% of medical institutions nationwide. By the end of 2005, approximately 22.7 million individuals had been enrolled in Taiwan's NHI program with a coverage rate of 98%. The NHI system in Taiwan contains the NHIRD which consists of data characterizing healthcare utilization of insured residents, including expenditures, medical procedures/treatments, and basic characteristics of patients, providers and physicians. The NHIRD uses the International Classification of Diseases, 9th revision, clinical modification diagnoses (ICD-9-CM).

In this study, the included subjects were identified from the NHIRD. The index date was defined as the date on which the subject was first prescribed an antidepressant for a diagnosis of depressive disorder in 2003. Data on all NHI information for each subject were extracted for the two-year period spanning the index date (one year preceding, and one year following).

2.2. Participants

All subjects in NHIRD meeting the following criteria were included:

- At least one prescription for an antidepressant for treatment of major depressive disorder (MDD) (ICD-9-CM codes: 296.2x, 296.3x) or minor depression (ICD-9-CM codes: 311.xx, 300.4x) in 2003.
- Data available for a minimum of 12 months before and after the index date.
- Age 18 years or over on the index date.

A subsample of patients with *newly-diagnosed depression* was also identified within this overall sample, which was operationally defined as individuals who were free of antidepressant use or a depression diagnosis for a minimum of 12 months before the index date.

2.3. Demographic and clinical information

Demographic and clinical data were extracted, including age, gender, diagnosis of depressive disorders, and initial choice of antidepressants on the index date. Participants were further grouped according to past treatment history, i.e., newly-diagnosed depression and non-newly-diagnosed depression.

Baseline characteristics were traced back for all subjects for the 12 months prior to the index date, including comorbid mental disorders, physical illnesses (CVD, diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), renal diseases, and cancer), PPS (backache, headache, musculoskeletal and gastrointestinal pain), and healthcare utilization/expenditure.

2.4. Service use and costs

Service use components extracted from the NHIRD included outpatient services, emergency attendances, and inpatient stays. Service use over the 12-month study period was described by the percentage of patients with at least one unit of service use and the mean number of service contacts for the whole sample. Medication use regarding prescriptions of antidepressants was identified. All costs over the 12-month study period were calculated from the actual claims data, were described by service categories, and expressed in 2003–4 US dollars.

2.5. Data analysis

Sociodemographic data, clinical characteristics, baseline healthcare utilization/expenditure, and initial antidepressant treatment were described for the overall sample and compared between newly-diagnosed depression and non-newly-diagnosed depression groups.

To identify characteristics predictive of healthcare costs over the 12-month period, a multivariate generalized linear regression model with a log link and gamma variance function was employed (McCullagh and Nelder, 1989). Separate models were run for total healthcare costs, psychiatric costs, and non-psychiatric costs. And to measure the model fit, the root mean square error (RMSE) (Zheng and Agresti, 2000) for each model was computed after excluding 0.1% of subjects with extremely large predicted values in costs. The independent variables considered in these models were age, sex, index depression diagnosis, past treatment history, initial choice of antidepressants, baseline comorbid mental/physical disorders, baseline PPS, and baseline total healthcare expenditure. These variables were first selected using a univariate model and those significant at the 5% level were included subsequently. A backward selection process was then applied to obtain the final multivariate model, using a 5% level of significance. Subsequently, such analyses were performed in a subsample of subjects with newly-diagnosed depression as they were a group which warrants further investigation. This was also to determine the influence of past treatment history on the findings from the overall sample.

As use of psychiatric emergency and/or inpatient services may be indicators for patients who require more intensive care, thus generating higher costs, we examined variations in use of these two key services in further analyses. With use of psychiatric emergency services and use of psychiatric inpatient services as dependent variables, independent variables were entered in a multivariate logistic regression with a forward LR (likelihood ratios) method to explore predictors of use over the 12-month study period. A p-value of 0.05 was considered significant for all statistical analyses, which were performed using SPSS version 17.0 (Chicago, IL, USA).

3. Results

A total of 216,557 adult individuals met the inclusion criteria, including a subsample of 84,577 persons with newly-diagnosed

depression. Table 1 shows that for the overall sample, 61.9% were females and 18.7% were aged 65 years or over on the index date. Regarding baseline comorbidities, 26.9% had CVD, 10.9% had DM, and 15.2% had COPD. Comorbid PPS rates were particularly high for both the overall sample and the subsample of individuals with newly-diagnosed depression. At the index visit, 45.6% of the overall sample were prescribed selective serotonin reuptake inhibitors (SSRIs) and 8.6% prescribed serotonin norepinephrine reuptake inhibitors (SNRIs). Only 3.1% of patients received other newer antidepressants (bupropion and mirtazapine).

Patients with newly-diagnosed depression were younger and had a greater proportion of females compared to those with non-newly-diagnosed depression. They had lower rates of comorbid physical/mental illnesses and lower prevalence of PPS. Health

Table 1
Sociodemographic and clinical characteristics of the overall sample and comparisons between newly-diagnosed and non-newly-diagnosed depression.[a]

	The overall sample (n = 216,557)	Newly-diagnosed depression (n = 84,577)	Non-newly-diagnosed depression (n = 131,980)
Age [mean (SD)]	47.4 (17.0)	43.9 (17.0)	49.7 (16.6)
Age categories [n (%)]			
>=85	1756 (0.8)	637 (0.8)	1119 (0.8)
75–84	13,626 (6.3)	4058 (4.8)	9568 (7.2)
65–74	25,019 (11.6)	7267 (8.6)	17,752 (13.5)
55–64	27,438 (12.7)	8787 (10.4)	18,651 (14.1)
45–54	44,252 (20.4)	15,520 (18.4)	28,732 (21.8)
35–44	46,692 (21.6)	18,115 (21.4)	28,577 (21.7)
25–34	36,338 (16.8)	17,740 (21.0)	18,598 (14.1)
18–24	21,436 (9.9)	12,453 (14.7)	8983 (6.8)
Sex [n (%)]			
Male	82,414 (38.1)	30,683 (36.3)	51,731 (39.2)
Female	134,143 (61.9)	53,894 (63.7)	80,249 (60.8)
Depression diagnosis at index visit [n (%)]			
Major depression	78,296 (36.2)	27,029 (32.0)	51,267 (38.8)
Minor depression	138,261 (63.8)	57,548 (68.0)	80,713 (61.2)
Baseline physical illnesses [n (%)]			
Cardiovascular disease	58,350 (26.9)	18,132 (21.4)	40,218 (30.5)
Diabetes mellitus	23,563 (10.9)	7198 (8.5)	16,365 (12.4)
Chronic obstructive pulmonary disease	32,898 (15.2)	10,886 (12.9)	22,012 (16.7)
Hyperlipidemia	23,249 (10.7)	7351 (8.7)	15,898 (12.0)
Hypertension	51,271 (23.7)	15596 (18.4)	35,675 (27.0)
Renal disease	11,854 (5.5)	3766 (4.5)	8088 (6.1)
Cancer	8864 (4.1)	2850 (3.4)	6014 (4.6)
Baseline painful physical symptoms [n (%)]			
Musculoskeletal	99,455 (45.9)	36,168 (42.8)	63,287 (48.0)
Back	69,981 (32.3)	25,036 (29.6)	44,945 (34.1)
Gastrointestinal	111,271 (51.4)	40,018 (47.3)	71,253 (54.0)
Headache/migraine/dizziness	88,164 (40.7)	29,996 (35.5)	58,168 (44.1)
Baseline mental illnesses [n (%)]			
Schizophrenia	8207 (3.8)	1538 (1.8)	6669 (5.1)
Other psychotic disorder	4650 (2.1)	775 (0.9)	3875 (2.9)
Substance related	6127 (2.8)	1081 (1.3)	5046 (3.8)
Alcohol related	1748 (0.8)	254 (0.3)	1494 (1.1)
Drugs related	1084 (0.5)	196 (0.2)	888 (0.7)
Bipolar spectrum disorder	3882 (1.8)	457 (0.5)	3425 (2.6)
Dementia	7356 (3.4)	1426 (1.7)	5930 (4.5)
Generalized anxiety disorder	11,718 (5.4)	2313 (2.7)	9405 (7.1)
Obsessive-compulsive disorder	3797 (1.8)	180 (0.2)	3617 (2.7)
Panic disorder	7388 (3.4)	588 (0.7)	6800 (5.2)
Phobic disorder	1742 (0.8)	131 (0.2)	1611 (1.2)
Post-traumatic stress disorder	404 (0.2)	20 (0.0)	384 (0.3)
Sleep disorder	52,001 (24.0)	15,196 (18.0)	36,805 (27.9)
Hyperkinetic syndrome	133 (0.1)	22 (0.0)	111 (0.1)
Baseline healthcare service use			
Number of outpatient visits [mean (SD)]	31.6 (24.8)	23.9 (20.9)	36.5 (25.8)
ER visit [n (%)]	74,970 (34.6)	26,178 (31.0)	48,792 (37.0)
Hospitalization [n (%)]	45,397 (21.0)	13,576 (16.1)	31,821 (24.1)
Total 12-month costs prior to index date [mean (SD)]	1365.6 (2397.2)	894.6 (2089.0)	16,67.5 (2529.6)
Index AD [n (%)]			
SSRI	98,791 (45.6)	42,476 (50.2)	56,315 (42.7)
SNRI	18,520 (8.6)	7549 (8.9)	10,971 (8.3)
Other newer AD	6759 (3.1)	3104 (3.7)	3655 (2.8)
TCA	18,787 (8.7)	5873 (6.9)	12,914 (9.8)
Flupentixol/melitracen	11,449 (5.3)	4341 (5.1)	7108 (5.4)
Other older AD	40,897 (18.9)	14,016 (16.6)	26,881 (20.4)
Multiple AD	21,354 (9.9)	7218 (8.5)	14,136 (10.7)

Baseline characteristics were measured over the 12-month pre-index period.
Costs were expressed in 2003–4 US dollars.
SD = standard deviation; AD = antidepressant; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant; other newer AD: bupropion and mirtazapine; other older AD: maprotiline, moclobemide, and trazodone.
[a] All comparisons between newly-diagnosed and non-newly-diagnosed depression were statistically significant with a $p < 0.001$ (chi-squared test was used for categorical variables and independent t-test for continuous variables).

Table 2
Service use and healthcare costs over the 12-month study period, overall sample.

Service use		
	n (% using)	Mean (SD)
Psychiatric outpatient	184,271 (85.1)	7.30 (7.72)
Psychiatric inpatient	10,916 (5.0)	0.08 (0.46)
Psychiatric emergency	3515 (1.6)	0.03 (0.42)
Non-psychiatric outpatient	212,327 (98.0)	27.48 (25.51)
Non-psychiatric inpatient	39,077 (18.0)	0.33 (0.98)
Non-psychiatric emergency	70,812 (32.7)	0.76 (3.13)
Healthcare costs ($, year 2003–4 values)		
		Mean (SD)
Psychiatric outpatient		356.64 (465.87)
Psychiatric inpatient		148.22 (992.87)
Psychiatric emergency		0.86 (9.84)
Non-psychiatric outpatient		744.02 (1927.52)
Non-psychiatric inpatient		437.02 (2423.54)
Non-psychiatric emergency		44.46 (171.97)
Total		1731.21 (3508.72)

service utilization at baseline was lower as well. A higher proportion of them were prescribed newer generation antidepressants.

3.1. Service use and costs

Service use data are summarized in Table 2. Of the overall sample, 85.1% had used psychiatric outpatient services over the 12-month study period. Over the same period, 5.0% of them had been admitted to psychiatric wards for inpatient treatment and 1.6% had psychiatric emergency attendances.

Costs of outpatient contacts in total accounted for 63.6% of total healthcare costs for these patients. And overall expenditures on psychiatric services were around 29.2% of the total healthcare costs.

3.2. Total healthcare costs

Table 3 reveals that higher total healthcare costs were associated with older age, male gender, an index diagnosis of MDD, non-newly-diagnosed depression, and having CVD, DM, COPD, renal disease, cancer or PPS at baseline.

Use of SNRIs, other newer generation antidepressants and use of multiple antidepressants were related to higher costs compared to use of SSRIs at the index date. Lower costs were observed for those using tricyclic antidepressants (TCAs), flupentixol/melitracen, and other older antidepressants (maprotiline, moclobemide, and trazodone). The analysis on the subsample of newly-diagnosed depression revealed similar results with those from the full sample. Regarding the model fit, RMSE of the model for total costs was 1316. The predicted mean of total costs was 1925 US dollars versus the actual mean costs 1731 US dollars.

Table 3
Multivariate analysis (GLM) of total healthcare costs over the 12-month study period.

	RR (95% CI)	
	The overall sample (n = 216,557)	Newly-diagnosed depression (n = 84,577)
Age	1.011 (1.011, 1.011)	1.013 (1.013, 1.014)
Sex		
Male	1.143 (1.134, 1.152)	1.231 (1.215, 1.247)
Female	1	1
Depression diagnosis at index visit		
Major depression	1.134 (1.125, 1.143)	1.160 (1.144, 1.176)
Minor depression	1	1
Past treatment history		
Newly-diagnosed depression	0.959 (0.952, 0.967)	–
Non-newly-diagnosed depression with history of both AD treatment and depression diagnosis	1.136 (1.121, 1.151)	–
Non-newly-diagnosed depression with history of either AD treatment or depression diagnosis	1	–
Index AD treatment		
SNRI	1.160 (1.144, 1.176)	1.144 (1.118, 1.170)
Other newer AD	1.142 (1.118, 1.166)	1.152 (1.114, 1.192)
TCA	0.905 (0.893, 0.918)	0.895 (0.872, 0.918)
Other older AD	0.956 (0.946, 0.965)	0.978 (0.960, 0.996)
Flupentixol/melitracen	0.876 (0.862, 0.891)	0.902 (0.876, 0.929)
Use of multiple ADs	1.177 (1.162, 1.192)	1.217 (1.189, 1.246)
SSRI	1	1
Baseline physical illnesses		
Cardiovascular disease		
Yes vs. No	1.180 (1.169, 1.191)	1.270 (1.248, 1.293)
Diabetes mellitus		
Yes vs. No	1.256 (1.240, 1.271)	1.315 (1.284, 1.347)
Chronic obstructive pulmonary disease		
Yes vs. No	1.122 (1.111, 1.134)	1.126 (1.104, 1.148)
Renal disease		
Yes vs. No	1.161 (1.142, 1.181)	1.230 (1.190, 1.270)
Cancer		
Yes vs. No	1.326 (1.302, 1.351)	1.478 (1.426, 1.532)
Baseline painful physical symptoms		
Musculoskeletal		
Yes vs. No	1.068 (1.060, 1.077)	1.069 (1.054, 1.084)
Back		
Yes vs. No	1.062 (1.053, 1.071)	1.069 (1.053, 1.085)
Gastrointestinal		
Yes vs. No	1.067 (1.059, 1.075)	1.059 (1.045, 1.073)
Headache/migraine/dizziness		
Yes vs. No	1.049 (1.040, 1.057)	1.046 (1.032, 1.061)
Baseline mental illnesses		
Schizophrenia		
Yes vs. No	1.890 (1.854, 1.927)	2.456 (2.342, 2.575)
Other psychotic disorder		
Yes vs. No	1.185 (1.156, 1.215)	1.368 (1.281, 1.461)
Substance related		
Yes vs. No	1.301 (1.271, 1.331)	1.323 (1.249, 1.401)
Alcohol related		
Yes vs. No	1.484 (1.423, 1.548)	1.662 (1.480, 1.867)
Drugs related		
Yes vs. No	1.188 (1.128, 1.251)	1.483 (1.301, 1.690)
Bipolar spectrum disorder		
Yes vs. No	1.233 (1.199, 1.267)	1.301 (1.194, 1.417)
Dementia		
Yes vs. No	1.281 (1.255, 1.308)	1.355 (1.289, 1.424)
Generalized anxiety disorder		
Yes vs. No	0.998 (0.982, 1.014)	0.996 (0.958, 1.035)
Obsessive-compulsive disorder		
Yes vs. No	1.069 (1.039, 1.099)	0.978 (0.854, 1.120)
Panic disorder		
Yes vs. No	0.961 (0.941, 0.980)	1.040 (0.964, 1.121)
Post-traumatic stress disorder		
Yes vs. No	1.190 (1.094, 1.293)	0.983 (0.655, 1.476)
Total 12-month costs prior to index date (1000 USD)	1.182 (1.179, 1.185)	1.175 (1.170, 1.181)

RR = relative risk; CI = confidence interval; AD = antidepressant; SNRI = serotonin norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant; SSRI = selective serotonin reuptake inhibitor; other newer AD: bupropion and mirtazapine; other older AD: maprotiline, moclobemide, and trazodone.

3.3. Non-psychiatric healthcare costs

Older age, and male gender were related to higher non-psychiatric costs in the following year (Table 4). Compared to patients with history of either an antidepressant treatment or a depression diagnosis, those with newly-diagnosed depression had higher non-psychiatric costs. Patients with an index diagnosis of MDD or a baseline comorbid mental disorder were associated with lower costs, with the only exceptions being alcohol, substance misuse, multiple drugs-related mental disorders and dementia. The presence of a comorbid physical illness or PPS at baseline was related to higher non-psychiatric costs.

Table 4
Multivariate analysis (GLM) of non-psychiatric costs and psychiatric costs over the 12-month study period, overall sample.

	RR (95% CI)	
	Non-psychiatric healthcare costs	Psychiatric healthcare costs
Age	1.019 (1.019, 1.020)	0.998 (0.997, 0.998)
Sex		
Male	1.073 (1.063, 1.082)	1.214 (1.201, 1.226)
Female	1	1
Depression diagnosis at index visit		
Major depression	0.978 (0.969, 0.987)	1.363 (1.349, 1.377)
Minor depression	1	1
Past treatment history		
Newly-diagnosed depression	1.110 (1.100, 1.121)	0.696 (0.689, 0.704)
Non-newly-diagnosed depression with history of both AD treatment and depression diagnosis	1.076 (1.060, 1.093)	1.359 (1.334, 1.385)
Non-newly-diagnosed depression with history of either AD treatment or depression diagnosis	1	1
Index AD treatment		
SNRI	0.995 (0.979, 1.011)	1.396 (1.372, 1.421)
Other newer AD	1.014 (0.988, 1.040)	1.323 (1.288, 1.360)
TCA	1.046 (1.029, 1.063)	0.709 (0.695, 0.723)
Other older AD	1.063 (1.051, 1.076)	0.841 (0.829, 0.853)
Flupentixol/melitracen	1.031 (1.011, 1.052)	0.681 (0.664, 0.699)
Use of multiple ADs	1.070 (1.054, 1.086)	1.434 (1.409, 1.458)
SSRI	1	1
Baseline physical illnesses		
Cardiovascular disease		
Yes vs. No	1.252 (1.238, 1.266)	1.015 (1.002, 1.029)
Diabetes mellitus		
Yes vs. No	1.362 (1.343, 1.382)	0.991 (0.974, 1.009)
Chronic obstructive pulmonary disease		
Yes vs. No	1.168 (1.153, 1.182)	1.004 (0.990, 1.019)
Renal disease		
Yes vs. No	1.245 (1.220, 1.270)	0.855 (0.835, 0.876)
Cancer		
Yes vs. No	1.562 (1.528, 1.597)	0.857 (0.835, 0.880)
Baseline painful physical symptoms		
Musculoskeletal		
Yes vs. No	1.132 (1.121, 1.143)	0.974 (0.963, 0.984)
Back		
Yes vs. No	1.120 (1.109, 1.131)	0.971 (0.960, 0.982)
Gastrointestinal		
Yes vs. No	1.163 (1.153, 1.174)	0.955 (0.945, 0.965)
Headache/migraine/dizziness		
Yes vs. No	1.088 (1.078, 1.098)	1.033 (1.022, 1.044)
Baseline mental illnesses		
Schizophrenia		
Yes vs. No	0.892 (0.871, 0.931)	3.443 (3.358, 3.531)
Other psychotic disorder		
Yes vs. No	0.966 (0.937, 0.996)	1.514 (1.465, 1.565)
Substance related		
Yes vs. No	1.335 (1.298, 1.372)	1.323 (1.282, 1.364)
Alcohol related		
Yes vs. No	1.467 (1.395, 1.544)	1.707 (1.614, 1.805)
Drugs related		
Yes vs. No	1.196 (1.124, 1.273)	1.208 (1.129, 1.292)
Bipolar spectrum disorder		
Yes vs. No	0.991 (0.958, 1.024)	1.649 (1.590, 1.709)
Dementia		
Yes vs. No	1.291 (1.260, 1.323)	1.451 (1.407, 1.496)
Generalized anxiety disorder		
Yes vs. No	1.007 (0.988, 1.026)	1.016 (0.994, 1.038)
Obsessive-compulsive disorder		
Yes vs. No	0.837 (0.809, 0.865)	1.241 (1.197, 1.286)
Panic disorder		
Yes vs. No	0.902 (0.881, 0.924)	1.062 (1.034, 1.090)
Post-traumatic stress disorder		
Yes vs. No	1.045 (0.946, 1.154)	1.229 (1.104, 1.368)
Total 12-month costs prior to index date (1000 USD)	1.200 (1.197, 1.203)	1.078 (1.074, 1.082)

RR = relative risk; CI = confidence interval; AD = antidepressant; SNRI = serotonin norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant; SSRI = selective serotonin reuptake inhibitor; other newer AD: bupropion and mirtazapine; other older AD: maprotiline, moclobemide, and trazodone.

Patients prescribed older antidepressants had higher non-psychiatric costs in the following year compared to those prescribed SSRIs while patients prescribed newer antidepressants such as SNRIs or bupropion/mirtazapine had non-psychiatric costs that did not differ significantly. The RMSE of the model was 4380. And the predicted mean of non-psychiatric costs was 1452 US dollars while the actual mean cost was 1226 US dollars.

3.4. Psychiatric healthcare costs

As shown in Table 4, male gender was associated with higher psychiatric costs in the following year. Not surprisingly, patients having an index diagnosis of MDD had increased costs as did those with baseline comorbid mental disorders. Patients with newly-diagnosed depression had lower psychiatric costs compared to those who had been diagnosed prior to the index date. Younger age was shown to be related to *higher* psychiatric costs.

Use of newer generation antidepressants or multiple antidepressants prescribed on the index date were related to higher psychiatric costs compared to those prescribed SSRIs, while use of older antidepressants was related to lower costs. Among comorbid physical illnesses, CVD was the only one found to increase psychiatric costs. And among PPS, only pain complaints relating to the central nervous system (CNS), i.e., headache/dizziness/or migraine, were related to higher psychiatric costs. The RMSE of the model was 1074. The predicted mean of psychiatric costs was 577 US dollars and the actual mean was 506 US dollars.

3.5. Use of psychiatric emergency and inpatient services

Younger age, male gender, a diagnosis of MDD or certain comorbid mental disorders were more likely to lead to psychiatric emergency attendances and hospitalizations (Table 5). CVD or COPD was related to higher odds of using psychiatric emergency and hospitalization services. Headache/dizziness/or migraine complaints at baseline were associated with an increase in the odds of using psychiatric emergency and hospitalization services as well.

4. Discussion

This study provided new evidence on the associations between comorbidities, service use, and healthcare costs for patients with depression. Although the nature of the associations differed across cost categories, the multivariate models revealed that age, gender,

Table 5
Multivariate logistic analysis for use of psychiatric inpatient and emergency services over the 12-month study period, overall sample.

	Or (95% CI)	
	Use of psychiatric inpatient services	Use of psychiatric emergency services
Age	0.974 (0.972, 0.975)	0.949 (0.947, 0.952)
Sex		
Male	1.689 (1.620, 1.762)	1.731 (1.613, 1.858)
Female	1	1
Depression diagnosis at index visit		
Major depression	1.909 (1.830, 1.991)	1.771 (1.650, 1.901)
Minor depression	1	1
Past treatment history		
Newly-diagnosed depression	1.093 (1.042, 1.147)	1.022 (0.943, 1.108)
Non-newly-diagnosed depression with history of both AD treatment and depression diagnosis	2.445 (2.310, 2.588)	1.593 (1.441, 1.762)
Non-newly-diagnosed depression with history of either AD treatment or depression diagnosis	1	1
Index AD treatment		
SNRI	1.385 (1.295, 1.481)	0.736 (0.642, 0.843)
Other newer AD	1.712 (1.558, 1.880)	1.007 (0.838, 1.209)
TCA	0.747 (0.680, 0.820)	0.831 (0.708, 0.974)
Other older AD	0.926 (0.872, 0.984)	1.169 (1.062, 1.287)
Flupentixol/melitracen	0.601 (0.525, 0.688)	1.300 (1.097, 1.540)
Use of multiple ADs	1.454 (1.365, 1.549)	1.388 (1.250, 1.543)
SSRI	1	1
Baseline physical illnesses		
Cardiovascular disease		
Yes vs. No	1.060 (1.003, 1.120)	1.292 (1.178, 1.417)
Chronic obstructive pulmonary disease		
Yes vs. No	1.080 (1.017, 1.147)	1.120 (1.010, 1.241)
Renal disease		
Yes vs. No	0.741 (0.667, 0.824)	–
Cancer		
Yes vs. No	0.773 (0.685, 0.873)	–
Baseline painful physical symptoms		
Headache/migraine/dizziness		
Yes vs. No	1.062 (1.016, 1.109)	1.125 (1.046, 1.211)
Baseline mental illnesses		
Schizophrenia		
Yes vs. No	4.271 (4.010, 4.548)	2.971 (2.688, 3.283)
Other psychotic disorder		
Yes vs. No	1.776 (1.616, 1.953)	1.594 (1.374, 1.848)
Substance related		
Yes vs. No	2.277 (2.099, 2.471)	1.982 (1.742, 2.255)
Alcohol related		
Yes vs. No	3.526 (3.112, 3.995)	2.014 (1.656, 2.449)
Drugs related		
Yes vs. No	1.257 (1.051, 1.502)	1.328 (1.038, 1.699)
Bipolar spectrum disorder		
Yes vs. No	2.453 (2.236, 2.691)	2.655 (2.321, 3.037)
Dementia		
Yes vs. No	1.817 (1.638, 2.015)	1.440 (1.172, 1.770)
Generalized anxiety disorder		
Yes vs. No	0.840 (0.759, 0.929)	–
Obsessive-compulsive disorder		
Yes vs. No	0.864 (0.757, 0.987)	1.278 (1.068, 1.529)
Panic disorder		
Yes vs. No	0.825 (0.736, 0.924)	1.478 (1.271, 1.718)
Total 12-month costs prior to index date (1000 USD)	1.059 (1.052, 1.067)	1.033 (1.021, 1.045)

OR = odds ratio; CI = confidence interval; AD = antidepressant; SNRI = serotonin norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant; SSRI = selective serotonin reuptake inhibitor; other newer AD: bupropion and mirtazapine; other older AD: maprotiline, moclobemide, and trazodone.

depression severity, past treatment history, comorbid mental/physical illnesses, PPS, and choice of initial antidepressants were all associated with healthcare costs in the following year. Factors including comorbid CVD and PPS were further explored to understand patterns of variation in psychiatric emergency and inpatient service use over the 12-month study period.

4.1. Demographic characteristics

Although previous studies have suggested that medical costs are higher for women than men (Owens, 2008; Woolhandler and Himmelstein, 2007), this study found a different result: for patients with depressive disorders, and taking into account other influences on costs, male gender was shown to be associated with higher costs for both non-psychiatric and psychiatric healthcare services.

There have been few recent studies that specifically examined the association between gender and healthcare utilization/expenditure for patients with depressive disorders. A study of elderly patients with psychiatric diagnoses suggested that men had more emergency attendances and had greater inpatient costs than women, which led some investigators to propose that when men eschew regular visits to physicians, it is likely that emergency or inpatient treatment may be required as illness progresses (Husaini et al., 2002). Consistently, male patients were shown to be associated with increased use of psychiatric emergency and inpatient services in the current study. One interpretation of our results is therefore that male patients with depression may enter the healthcare system later in the disease course, by which time their illness is more severe, thus generating higher costs.

4.2. Comorbid cardiovascular disease

Among the frequently co-occurring physical illnesses considered in this study, CVD was the only one shown to increase not only non-psychiatric but also psychiatric costs. Depression has been revealed to be an independent risk factor for the future onset, progression, and recurrence of CVD (Carney et al., 1988; Ferketich et al., 2000; Nicholson et al., 2006; Rugulies, 2002; Sesso et al., 1998; Wassertheil-Smoller et al., 2004), which can be mediated both by poor health behavior and by the pathophysiological correlates of depressive symptoms, e.g., neuroendocrine and inflammatory activation (Frasure-Smith and Lesperance, 2010; Rozanski et al., 2005). Additionally, individual antidepressants have a wide range of cardiovascular effects which may affect cardiovascular-related morbidity and mortality (Coupland et al., 1997; Taylor, 2008; Vieweg and Wood, 2004); it seems likely that the co-existence of CVD and depression may impact patients' physical conditions and their non-psychiatric costs.

As well, we found that the presence of comorbid CVD was related to higher odds of using both psychiatric emergency and hospitalization services which was consistent with the finding of increased psychiatric costs in these patients. CVD has been shown to be correlated with certain lifestyles, alcohol consumption, and personality traits (e.g., Type D personality), some of which seem to be highly correlated with use of psychiatric services. For instance, Type D has been conceptualized as a personality trait comprising negative affectivity and social inhibition that often co-occurs with depression in patients with coronary artery disease, and that may inhibit remission of depressive symptoms (Albus et al., 2011; Denollet et al., 2010). Although it can only be speculative, the identified association between the presence of CVD and increased psychiatric service utilization/expenditure in this study may be understood as being indirectly influenced by these unmeasured and potentially associated factors.

4.3. Painful physical symptoms

The relationships between depression and pain are complex with similar brain areas regulating both mood and the affective

components of pain (Giesecke et al., 2005). High prevalence of pain complaints has been reported in patients with depression (Bair et al., 2003; Husain et al., 2007; Ohayon and Schatzberg, 2003). Our results added to this evidence in finding a high percentage of comorbid PPS in patients with newly-diagnosed depression, which supports findings from previous studies that pain usually appears before the development of MDD (Ohayon and Schatzberg, 2010). On the other hand, increasing pain interference has been reported to be associated not only with higher odds of having depressive disorders (Barry et al., 2012), but also with adverse impact on poor treatment response (Bair et al., 2004). Pain complaints seem to be characteristic of depression that is more severe and refractory to antidepressant treatments, as evidenced by higher healthcare utilization, and higher costs (Gameroff and Olfson, 2006).

As most previous studies were based on highly selective samples and did not consider many comorbidities, it is unclear whether these results could be generalized to larger samples of patients in a real-world setting, and to what extent other factors such as comorbid mental/physical illnesses would contribute to the possible association between PPS, healthcare utilization, and treatment outcome. In the current study, we concurred with previous studies in suggesting that the presence of PPS was associated with higher total healthcare costs in the following year; this remained true for those with newly-diagnosed depression. In addition, analyses based on origins of pain complaints found that the co-existence of PPS was generally associated with higher non-psychiatric costs but lower psychiatric costs, with headache being the only exception: unlike pain complaints over other somatic systems, having headache was associated with higher psychiatric costs and greater odds of using psychiatric emergency and inpatient services. A recent study suggested the existence of differences in separate pain modalities in relation to depression, and that a closer relationship may exist between MDD and neuropathic pain than non-neuropathic pain (Ohayon and Stingl, 2012). It seems possible that a more direct relationship might exist between depression and pain complaints over the central nervous system than PPS from other somatic systems as our data might suggest.

4.4. Antidepressant choice

The current study showed that initial choice of antidepressants appears to be associated with total healthcare costs in the following year. Compared to patients prescribed SSRIs, those prescribed older antidepressants had lower total and psychiatric costs, whilst patients prescribed SNRIs, and other newer antidepressants had higher total and psychiatric costs. However, to a large extent these differences may be attributed to physician selection: patients prescribed older antidepressants were more likely to suffer minor depression, to be older, and to have more PPS and physical comorbidities at baseline. Contrarily, patients prescribed newer antidepressants were more likely to have MDD, to be younger, and to have fewer baseline physical comorbidities (not shown in this paper). These distinctive characteristics suggest the existence of physician selection based on patients' clinical characteristics that unfortunately could not be fully accounted for by the adjustment factors in our analyses.

Further support could be drawn from the comparisons between cost models: as seen in Table 4, patients prescribed SNRIs and other newer antidepressants were similar to those prescribed SSRIs in non-psychiatric costs, whilst patients prescribed TCAs and other older antidepressants generally had higher non-psychiatric costs. These results could be interpreted as showing that there were differences especially in physical comorbidities between these two groups of depressed patients. Previous database analyses have also suggested that SSRI users may have higher depression-related service expenditures but lower non-depression-related service expenditures than TCA users (Pan et al., 2012). Along with these previous findings, our results suggest that depressed patients prescribed older antidepressants may be different from those prescribed SSRIs, SNRIs, and other newer antidepressants in terms of clinical features of depression and comorbidities.

4.5. Limitations and conclusions

As service use data contained in the NHIRD includes only health services provided by the NHI system in Taiwan, the perspective of the current analysis was relatively limited, and we were not able to analyze wider economic impacts. Confounding or selection bias due to the nonrandomized study design should be borne in mind while interpreting the results, although the real-world context and whole-country coverage are strengths, especially when analyzing the inherent heterogeneity of clinical presentations and patient characteristics and their influences on help-seeking behaviors, clinical outcomes, and costs.

In conclusion, the current study—based on a large national database—suggests a set of significant correlates of healthcare costs for depressed patients. Male gender and a diagnosis of MDD were significantly associated with higher total healthcare costs. The baseline comorbidities of CVD and headache were associated not only with higher non-psychiatric but also with higher psychiatric costs; moreover, these comorbidities were related to increased use of psychiatric emergency and inpatient services in the following year.

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Contributors

Dr. Pan, Prof. McCrone and Prof. Knapp designed the study. Dr. Pan managed the literature searches, statistical analyses, and wrote the first draft of the manuscript. Prof. Yeh and Ms. Chen undertook part of the data analyses. All authors contributed to and have approved the final manuscript.

Conflict of interest

Prof. Knapp has acted as consultant and speaker for Lundbeck and Bristol Myers Squibb, and has had research funding from Janssen. Prof. McCrone has received speaker and consultancy fees from Lundbeck, Bristol Myers Squibb, Lilly and Janssen-Cilag. All other authors have reported that they have no conflicts of interest over the past five years to report as related to the subject of the report.

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ORIGINAL ARTICLE

Impact of initial treatment outcome on long-term costs of depression: a 3-year nationwide follow-up study in Taiwan

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Background. The impact of initial treatment outcome on long-term healthcare costs in depression remains to be determined. We aimed to identify demographic and clinical characteristics associated with initial treatment outcomes and to test whether and how these outcomes influence total healthcare costs over the subsequent 3 years.

Method. In this secondary analysis of a large healthcare database, a national cohort of adult patients (n=126 471) who received antidepressant treatment for depression was identified and factors associated with initial outcomes were examined. Potential predictors of total healthcare costs in the subsequent years were assessed using generalized linear modeling, with a particular focus on initial outcome status after antidepressant treatment and co-morbidities.

Results. Depression type and co-morbid painful physical symptoms (PPS) or mental illnesses were found to be associated with initial outcome status. Having sustained treatment-free status after initial treatment was shown to be associated with a 22–33% reduction in total healthcare costs in the second and third years (compared to those with late recontacts). Although the presence of co-morbid PPS was associated with higher healthcare costs, having certain co-morbid anxiety disorders was associated with lower costs over the 3 years.

Conclusions. Initial outcome status after antidepressant treatment has a sustained impact on individuals' total healthcare costs over the following 3 years. Future efforts to improve initial treatment outcome of depression are warranted.

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Key words: Cost, depression, longitudinal study, treatment outcome.

Introduction

Depressive disorders are a leading cause of burden among all diseases globally, accounting for 9.6% of all years lived with disability (YLDs) (Vos *et al.* 2012). To promote individual and population health and to reduce YLDs, it is crucial to improve patients' treatment outcomes and health states during and after treatment for depression. Moreover, given the high prevalence and chronic/relapsing course of depression, healthcare costs can pose a great barrier to its treatment. An association between depression and increased levels of health-service use and costs has been demonstrated (Simon *et al.* 1995; Katon, 2003), but much less is known about how this relationship is influenced by treatment outcomes. Data from longitudinal studies suggest that costs are significantly lower for patients who experience remission after the acute treatment phase than for those with less favorable outcomes (Simon *et al.* 2006; Sobocki *et al.* 2006; Sicras-Mainar *et al.* 2010*a*). However, the existing literature is limited in several ways. First, findings were based on relatively small samples (Simon *et al.* 2006; Sobocki *et al.* 2006). Second, the duration over which study subjects were followed up was limited to 6 to 12 months, and so the impact of initial treatment outcome on service use and costs beyond this point is unknown. Third, many of the studies tested for outcome (e.g. remission) at a point when a large proportion of participants would still be receiving antidepressants, thus leaving the impacts after cessation of antidepressant treatments largely undetermined.

In this study, we aimed to assess the longer-term economic impacts of outcome status following initial treatment for depression using claims data from

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a large national cohort of patients with depression from the National Health Insurance Research Database (NHIRD) in Taiwan. Type of depression, past treatment history, co-morbid mental/physical illnesses, painful physical symptoms (PPS) and choice of initial antidepressants have been found to be associated with healthcare costs and service use for patients treated for depression in Taiwan (Pan *et al.* 2013*a*), hence the cost analysis conducted in the current study has taken these factors into account. Specific objectives of this study were to explore factors associated with initial outcome status and to examine healthcare costs over the following 3 years relative to this status.

Method

Data

Data were extracted from the NHIRD in Taiwan. On 1 March 1995, Taiwan launched the compulsory single-payer NHI program to centralize the disbursement of healthcare funds and guarantee equal access to health care for all citizens; since 2000, the NHI coverage rate has exceeded 96%. Patients can enjoy free choice of providers and have direct access to specialist care without going through a gatekeeper or referral system. There is also no limit to the number of visits a patient can have (Chen *et al.* 2007). The NHI program uses the NHIRD, which consists of data files characterizing healthcare utilization of insured residents in Taiwan, including expenditures, medical procedures/treatments and basic characteristics of patients, providers and physicians. The NHIRD uses the ICD, 9th revision, clinical modification (ICD-9-CM) diagnoses. The index date for our study was defined as the date on which the subject was first prescribed an antidepressant for a diagnosis of depressive disorders in 2003. Data regarding service use and costs for the 3 years following the index date were extracted.

Participants

All insured subjects of the NHI system in Taiwan meeting the following criteria were included: (*a*) age $\geqslant$18 years on the index date; (*b*) at least one prescription for an antidepressant for treatment of major depressive disorder (MDD: ICD-9-CM codes 296.2x and 296.3x) or other depressive disorders (ICD-9-CM codes 300.4x and 311.xx) in 2003; (*c*) at least three antidepressant prescriptions within the first 3 months of the index date; and (*d*) data available for a minimum of 12 months before and a minimum of 36 months after the index date.

Definition of initial outcome status

In this study, proxy criteria of treatment outcomes were operationally defined, which focused on the cessation of antidepressant treatment. This proxy measure has been validated by evaluating the concordance between remission as defined by antidepressant cessation for at least 6 months and remission determined by clinical criteria; the level of concordance between the two approaches was considered acceptable [Cronbach's α=90.6%, 95% confidence interval (CI) 85.6–95.6] (Sicras-Mainar *et al.* 2010*b*). This proxy measure of remission was also used in a recent economic evaluation for patients with depression (Byford *et al.* 2011).

However, to prevent confusion from actual remission defined by clinical rating scales, in this study we adopted the more descriptive term 'treatment-free status' instead of 'remission'. Additionally, in our recent study addressing attrition and treatment outcomes, 'sustained treatment-free status' was defined as further requiring no restart of antidepressant treatments (late recontacts) during the 18-month follow-up period (Pan *et al.* 2013*b*). We also specified that only participants who had at least three antidepressant prescriptions in the first 3 months were included to ensure that we were identifying a group of depressed patients with initial presentation that justified antidepressant treatment.

Study participants were therefore grouped according to three treatment outcomes:

(1) Sustained treatment-free status: patients who had antidepressant cessation for at least 6 months and had not restarted antidepressant use by the end of the 18-month observation period.
(2) Continuous treatment: patients who had not had cessation of antidepressant use for at least 6 months by the end of the 18-month observation period.
(3) Late recontacts: patients who had achieved antidepressant cessation for at least 6 months but later restarted antidepressant use during the 18-month period of observation.

Observation period for treatment outcome status

For each individual, the observation period started on the index date and continued for 18 months after this index date. The additional 6 months after the first 12 months was included to ensure there was adequate time to assess whether treatment-free status had been achieved, given the definition described earlier. The treatment-free period (i.e. cessation of antidepressant treatment) could start at any point during the 12 months after the index date, but a participant

needed to remain off antidepressants for a minimum of 6 months to meet the definition. Hence, an observation period of 18 months was required.

Demographic and clinical information

Demographic and clinical data, including age, gender, index diagnosis of depressive disorders and initial choice of antidepressants, were extracted. Provider information and clinical setting at the initial visit were also extracted. Participants were grouped according to past treatment history: newly diagnosed depression (defined as people who had not received antidepressant treatment or a depression diagnosis in the 12 months before the index date) and non-newly diagnosed depression.

Baseline characteristics were collected regarding co-morbid mental disorders, physical illnesses (cardiovascular disease, diabetes mellitus, chronic obstructive pulmonary disease, renal diseases and cancer), PPS (headache, backache, musculoskeletal and gastrointestinal pain and others) and also healthcare utilization/expenditure during the 12 months prior to the index visit.

Service use and costs

Service use data extracted from the NHIRD included contacts with out-patient services, emergency attendances and in-patient stays (for all reasons). The percentage of patients with at least one unit of service use and the mean number of service contacts were reported in this study. Annual service costs were calculated from the actual claims data, were converted by purchasing power parity (PPP) conversion rates (IMF, 2013) and are expressed in international dollars.

Statistical analyses

Sociodemographic data, clinical characteristics, baseline co-morbidities and initial choice of antidepressants were described and compared between groups by initial outcome status. Service use and costs of groups based on outcome status were also described by service categories and compared for the next 3 years after the index date.

To identify characteristics predictive of initial outcome status, a multinomial logistic regression analysis was performed, with outcome status as the dependent variable. The independent variables included age, sex, depression type, past treatment history, physician specialty, clinical settings at index visit, initial choice of antidepressants, baseline co-morbid mental/physical disorders and baseline PPS.

A multivariate generalized linear model regression with a log link and gamma variance function was used (McCullagh & Nelder, 1989) to examine the effects of outcome status on total healthcare costs while adjusting for other independent factors. Besides the regression model for the first year, separate models were run for the second-year and third-year total healthcare costs respectively, to further explore impacts of initial outcome status on future healthcare costs over the longer-term follow-up. Considering potential issues of multiple comparisons, a stringent significance criterion of $p<0.01$ was adopted for all statistical analyses, which were performed using Stata version 11.1 (StataCorp LP, USA).

Results

A total of 126 471 adult individuals met the inclusion criteria. Of these, 34.1% ($n=43\,065$) were classified as achieving sustained treatment-free status after initial treatment, 56.6% ($n=71\,543$) were continuously on antidepressant treatment, and another 9.4% ($n=11\,863$) had cessation of antidepressants for 6 months and later recontacts during the 18-month observation period.

Table 1(for a full version of this table see Table S1 in the online supplementary material) reveals notable differences between groups by initial outcome status, with the largest difference noted for past treatment history. Table 2 shows that there were significant differences in the use services and costs between the three groups; these differences remained robust until the end of the 3-year follow-up. Although service use and costs in the first year were comparable between the groups, these measures for patients initially achieving sustained treatment-free status decreased sharply in the second and third years and were much lower than the other groups. Those initially not achieving sustained treatment-free status contributed to 67.2% of the total costs for the whole study cohort, and to 77.6% and 76.8% in the second and third years respectively.

Factors associated with initial outcome status

Table 3 shows that patients who had MDD were more likely to be continuously on antidepressant treatment whereas newly diagnosed depression was associated with the other outcomes. Patients with a history of both antidepressant treatment and a diagnosis of depression were the most likely to be on continuous treatment. Being diagnosed with MDD and being prescribed antidepressant treatment by a psychiatrist (compared to other physicians) were also associated with higher odds of being continuously on antidepressant treatment.

Having certain kinds of PPS (i.e. backache, musculoskeletal or gastrointestinal pain) were each associated

Table 1. *Demographic and clinical characteristics at index visit*[a]

Characteristics	Sustained treatment-free status (n=43 065)	Continuous treatment (n=71 543)	Late recontact (n=11 863)
Male	17 129 (39.8)	28 326 (39.6)	4316 (36.4)
MDD diagnosis (depression type)	15 321 (35.6)	30 682 (42.9)	4524 (38.1)
Psychiatrist (physician type)	33 658 (78.2)	59 224 (82.8)	9599 (80.9)
Clinical setting			
Out-patient	41 317 (95.9)	69 339 (96.9)	11 483 (96.8)
Emergency service	220 (0.5)	221 (0.3)	51 (0.4)
In-patient	1528 (3.5)	1983 (2.8)	329 (2.8)
Index AD treatment			
SNRI	3899 (9.1)	6465 (9.0)	1027 (8.7)
Other newer AD[b]	1538 (3.6)	2308 (3.2)	365 (3.1)
TCA	3411 (7.9)	6729 (9.4)	1031 (8.7)
Other older AD[c]	7708 (17.9)	13 919 (19.5)	2091 (17.6)
Flupentixol/melitracen	2233 (5.2)	2716 (3.8)	601 (5.1)
Use of multiple ADs	3971 (9.2)	9573 (13.4)	1175 (9.9)
SSRI	20 305 (47.1)	29 833 (41.7)	5573 (47.0)

MDD, Major depressive disorder; AD, antidepressant; SNRI, serotonin norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor.

[a] The χ^2 test was used: all comparisons between groups by initial outcome statuses were statistically significant at a $p<0.001$.

[b] Bupropion and mirtazapine.

[c] Maprotiline, moclobemide and trazodone.

Values given as n (%).

with higher odds of having late recontacts. The presence of co-morbid mental illnesses tended to be associated with higher odds of being on continuous treatment, with dementia being the only exception (associated with higher odds of sustained cessation of antidepressant treatment).

Factors associated with total costs in the subsequent years

Models for total healthcare costs over the subsequent 3 years (Table 4) revealed that patients who experienced sustained treatment-free status after initial treatment had 33% lower costs in the second year and 22% lower costs in the third year compared to patients who experienced late recontacts.

In these models, patients who were diagnosed by non-psychiatrists on the index date had higher total costs for the subsequent 3 years, as were those diagnosed when they were in-patients. It is notable that, in the second and third years, total healthcare costs did not differ between patients prescribed selective serotonin reuptake inhibitors (SSRIs) and older-generation antidepressants. The presence of physical co-morbidities and PPS were associated with higher costs for all 3 years. Having co-morbid mental illnesses was generally associated with higher total costs, with exceptions being generalized anxiety disorder (GAD), panic disorder and phobic disorder, which were associated with lower costs.

Discussion

This study has added to the evidence base that initial treatment outcomes can impact total healthcare costs over the longer term. Specifically, patients who experienced sustained treatment-free status from initial treatment were found to have lower costs in the second and third years, compared to those with less favorable outcomes. In addition, treatment outcomes and total costs over time differed by initial choice of antidepressants in addition to the presence of co-morbid mental disorders and PPS.

The impact of initial outcome status

The focus in this study on sustained treatment-free status is relevant in assessing the impacts of initial outcome status over a longer-term follow-up given a high relapse/recurrence rate within the first 6 to 12 months of follow-up (Shapiro & Keller, 1981; Lin *et al.* 1998; Paykel, 1998). Only 30% of recovered patients were

Table 2. *Service use and costs over the 3-year period*[a]

	Sustained treatment-free status (n=43 065)		Continuous treatment (n=71 543)		Late recontact (n=11 863)	
Service use	% using	Mean (S.D.)[b]	% using	Mean (S.D.)[b]	% using	Mean (S.D.)[b]
The first year						
Psychiatric out-patient	84.6	6.63 (6.27)	89.2	12.79 (8.52)	87.5	7.43 (6.71)
Psychiatric in-patient	5.9	0.09 (0.43)	7.3	0.13 (0.60)	6.0	0.10 (0.46)
Psychiatric emergency	2.2	0.04 (0.50)	2.2	0.04 (0.47)	2.1	0.04 (0.72)
Non-psychiatric out-patient	98.0	26.42 (24.10)	98.2	30.46 (28.16)	98.6	30.56 (27.55)
Non-psychiatric in-patient	21.3	0.42 (1.15)	18.3	0.32 (0.95)	19.7	0.35 (0.98)
Non-psychiatric emergency	35.2	0.79 (2.53)	33.6	0.88 (4.37)	35.5	0.85 (2.33)
The second year						
Psychiatric out-patient	27.1	2.00 (5.06)	85.4	10.37 (8.56)	78.4	6.60 (7.55)
Psychiatric in-patient	1.5	0.02 (0.23)	5.0	0.09 (0.51)	4.9	0.08 (0.42)
Psychiatric emergency	0.7	0.01 (0.33)	1.6	0.03 (0.53)	1.6	0.03 (0.45)
Non-psychiatric out-patient	90.3	24.26 (24.62)	97.8	31.60 (29.28)	98.3	32.02 (28.83)
Non-psychiatric in-patient	14.2	0.24 (0.81)	18.7	0.33 (0.96)	19.2	0.35 (1.00)
Non-psychiatric emergency	25.6	0.49 (1.38)	33.5	0.87 (4.00)	35.4	0.89 (2.72)
The third year						
Psychiatric out-patient	28.2	2.33 (5.46)	76.4	9.13 (8.89)	59.6	5.32 (7.28)
Psychiatric in-patient	1.7	0.03 (0.24)	4.6	0.08 (0.46)	3.4	0.06 (0.37)
Psychiatric emergency	0.7	0.02 (0.33)	1.5	0.03 (0.42)	1.4	0.03 (0.37)
Non-psychiatric out-patient	88.0	22.70 (23.42)	95.3	30.14 (28.15)	95.7	29.07 (26.95)
Non-psychiatric in-patient	12.8	0.22 (0.80)	17.4	0.30 (0.92)	16.3	0.29 (0.92)
Non-psychiatric emergency	23.6	0.46 (1.50)	31.3	0.79 (3.23)	30.4	0.72 (2.67)
Healthcare costs[c]		Mean (S.D.)		Mean (S.D.)		Mean (S.D.)
The first year						
Psychiatric out-patient		464.99 (553.93)		1139.45 (947.58)		524.62 (568.87)
Psychiatric in-patient		255.33 (1588.13)		364.86 (1956.39)		290.05 (1811.71)
Psychiatric emergency		1.74 (17.15)		1.99 (20.01)		1.91 (21.26)
Non-psychiatric out-patient		1236.20 (2491.82)		1469.44 (4440.36)		1331.53 (2456.17)
Non-psychiatric in-patient		1236.20 (6086.22)		526.14 (2403.05)		589.58 (2747.11)
Non-psychiatric emergency		87.59 (258.85)		79.74 (364.09)		79.97 (240.80)
Total		3282.04 (7143.48)		3581.62 (5886.44)		2817.67 (4585.09)
The second year						
Psychiatric out-patient		126.63 (424.18)		940.46 (952.99)		494.09 (684.41)
Psychiatric in-patient		95.32 (1102.80)		287.67 (1821.63)		257.01 (1761.05)
Psychiatric emergency		0.73 (12.33)		2.06 (25.10)		1.76 (21.50)
Non-psychiatric out-patient		1040.82 (2395.60)		1481.47 (4861.05)		1374.46 (2432.50)
Non-psychiatric in-patient		652.49 (4090.22)		791.01 (4416.81)		823.52 (5106.10)
Non-psychiatric emergency		49.90 (190.85)		83.60 (278.42)		84.52 (244.86)
Total		1965.89 (5175.87)		3586.28 (7327.98)		3035.37 (6277.77)
The third year						
Psychiatric out-patient		172.36 (517.78)		861.70 (1046.36)		452.90 (779.66)
Psychiatric in-patient		110.64 (1226.52)		291.75 (1943.95)		216.26 (1721.74)
Psychiatric emergency		0.92 (14.80)		2.08 (26.67)		1.86 (23.35)
Non-psychiatric out-patient		1051.93 (2525.14)		1470.94 (2843.33)		1345.12 (2705.43)
Non-psychiatric in-patient		613.92 (4084.97		824.14 (4565.86)		688.09 (3427.75)
Non-psychiatric emergency		53.28 (199.43)		87.98 (293.08)		81.06 (290.45)
Total		2003.07 (5305.59)		3538.61 (6159.07)		2785.30 (5142.88)

S.D., Standard deviation.

[a] The χ^2 test was used for categorical variables and ANOVA for continuous variables: all comparisons between groups by initial outcome status were statistically significant at $p<0.001$ with the exceptions being percentage using, mean number of use, and costs for the first-year psychiatric emergency services.

[b] Number of contacts.

[c] Healthcare costs are expressed in international dollars: the first year in 2003–2004 international dollars; the second year in 2004–2005 international dollars; and the third year in 2005–2006 international dollars.

Table 3. *Multinomial logistic analysis for sustained treatment-free status and late recontact (versus continuous treatment)*

	Sustained treatment-free status	Late recontact
Age group (years) (*v.* 18–24)		
⩾85	0.601 (0.500–0.723)**	0.458 (0.325–0.644)**
75–84	0.402 (0.367–0.441)**	0.423 (0.365–0.492)**
65–74	0.337 (0.311–0.365)**	0.440 (0.388–0.499)**
55–64	0.354 (0.327–0.382)**	0.490 (0.435–0.552)**
45–54	0.381 (0.355–0.408)**	0.508 (0.456–0.566)**
35–44	0.428 (0.400–0.459)**	0.576 (0.518–0.640)**
25–34	0.634 (0.591–0.681)**	0.750 (0.672–0.837)**
Sex		
Male *v.* Female	1.014 (0.979–1.050)	0.897 (0.849–0.948)**
Depression type		
Major depression *v.* Other depression	0.809 (0.781–0.839)**	0.870 (0.823–0.919)**
Past treatment history[a]		
Newly diagnosed depression	3.336 (3.212–3.465)**	2.114 (1.992–2.243)**
Non-newly diagnosed depression with history of both AD treatment and depression diagnosis	0.794 (0.750–0.840)**	0.833 (0.764–0.909)**
Physician type		
Non-psychiatrist *v.* Psychiatrist	1.448 (1.383–1.515)**	1.199 (1.116–1.289)**
Clinical setting (*v.* In-patient)		
Out-patient	0.889 (0.806–0.981)*	1.023 (0.871–1.203)
Emergency service	0.969 (0.732–1.282)	1.099 (0.712–1.697)
Index AD treatment (*v.* SSRI)		
SNRI	0.906 (0.853–0.963)**	0.854 (0.777–0.940)**
Other newer AD[b]	0.947 (0.862–1.040)	0.815 (0.700–0.948)**
TCA	0.851 (0.799–0.907)**	0.885 (0.804–0.975)*
Other older AD[c]	0.889 (0.848–0.932)**	0.854 (0.793–0.919)**
Flupentixol/melitracen	1.271 (1.170–1.381)**	1.208 (1.065–1.369)**
Use of multiple ADs	0.649 (0.612–0.687)**	0.671 (0.614–0.733)**
Presence of baseline physical illnesses		
Chronic obstructive pulmonary disease	1.009 (0.962–1.058)	1.043 (0.969–1.122)
Diabetes mellitus	1.035 (0.980–1.093)	1.002 (0.919–1.091)
Renal disease	1.170 (1.088–1.259)**	1.055 (0.940–1.184)
Cancer	1.232 (1.136–1.336)**	1.106 (0.972–1.258)
Cardiovascular disease	0.990 (0.949–1.033)	1.012 (0.948–1.080)
Presence of baseline PPS		
Headache/migraine/dizziness	0.973 (0.939–1.010)	1.030 (0.974–1.089)
Back	1.000 (0.962–1.040)	1.116 (1.052–1.184)**
Musculoskeletal	1.040 (1.003–1.078)*	1.063 (1.005–1.125)*
Gastrointestinal	1.022 (0.986–1.058)	1.068 (1.011–1.128)*
Others	1.025 (0.962–1.091)	1.053 (0.959–1.157)
Presence of baseline mental illnesses		
Schizophrenia	0.719 (0.660–0.783)**	0.744 (0.651–0.850)**
Other psychotic disorders	0.917 (0.822–1.023)	0.885 (0.744–1.052)
Substance related	0.874 (0.786–0.972)*	1.003 (0.857–1.175)
Alcohol related	1.153 (0.956–1.390)	1.270 (0.963–1.674)
Drugs related	1.107 (0.884–1.387)	0.978 (0.682–1.403)
Bipolar spectrum disorder	0.784 (0.694–0.887)**	0.843 (0.701–1.013)
Dementia	1.166 (1.069–1.272)**	0.864 (0.740–1.008)
GAD	0.904 (0.840–0.973)**	0.938 (0.840–1.046)
Obsessive–compulsive disorder	0.688 (0.606–0.781)**	0.998 (0.841–1.186)
Panic disorder	0.689 (0.626–0.758)**	0.881 (0.771–1.006)
Phobic disorder	0.741 (0.615–0.893)**	0.784 (0.592–1.038)

Table 3 (*cont.*)

	Sustained treatment-free status	Late recontact
Post-traumatic stress disorder	0.891 (0.614–1.291)	0.787 (0.440–1.409)
Sleep disorder	0.918 (0.882–0.955)**	1.038 (0.977–1.102)
Attention deficit hyperactivity disorder	0.884 (0.461–1.696)	0.594 (0.176–2.007)

AD, Antidepressant; SNRI, serotonin norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor; PPS, painful physical symptoms; GAD, generalized anxiety disorder.

[a] Reference group is non-newly diagnosed depression with history of either AD treatment or depression diagnosis.

[b] Bupropion and mirtazapine.

[c] Maprotiline, moclobemide and trazodone.

Values given as odds ratio (99% confidence interval).

* $p<0.01$, ** $p<0.001$.

reported to remain in recovery during a previous 1-year follow-up (Keller & Shapiro, 1981). Rather than having a sustained recovery, a recent study also emphasized that 85% of out-patients with MDD have a chronic and/or recurrent course (Rush *et al.* 2012). It is thus important to evaluate the effect of sustained treatment-free status while taking into account both early relapses/recurrences and chronic depression under continuous treatment.

Based on the same proxy measure of outcomes, previous studies have shown that 12-month costs were significantly lower for remitters than non-remitters (Sicras-Mainar *et al.* 2010*a*; Byford *et al.* 2011), but beyond this point, the impact of outcome status on healthcare costs has remained less clear. In the current study, patients who achieved sustained treatment-free status had lower total costs in the second and third years compared to those with other initial outcomes, indicating an effect of initial outcome on total healthcare costs over a prolonged period of time. In addition, the evidence from previous studies has been limited to examining service use and costs in the first 6 or 12 months following initial treatment, and these are likely to be linked to the treatment that may have led to the outcomes. We found that first-year costs were higher for those patients achieving sustained treatment-free status than for those who experienced late recontacts (Table 2). An interpretation of this result could be that the higher total first-year costs for those achieving sustained treatment-free status may be due to the treatment required to achieve the outcome status, which then reduces costs in subsequent years. On the contrary, patients with insufficient treatment in the first year may then have higher costs subsequently as a result of not experiencing sustained treatment-free status. As shown in Table 2, those not achieving sustained treatment-free status contributed to 67.2% of the total costs for the whole study cohort in the first year, and this increased to 77.6% and 76.8% in the second and third years respectively.

Depression type, choice of initial antidepressants and other clinical characteristics

Our results suggest that the nature of depressive disorders is important for determining treatment outcomes (Sobocki *et al.* 2006). For instance, a diagnosis of MDD, being diagnosed by a psychiatrist, or the presence of a prior history of treatment/or a diagnosis can be indicators of greater disease severity or chronic/relapsing course and thus poorer outcome. However, non-psychiatric medical conditions constitute an important driver of total healthcare costs. Patients initially diagnosed in in-patient settings or diagnosed by a non-psychiatrist, possibly implying the presence of medical conditions, had higher total healthcare costs for each of the 3 years during the follow-up, along with increased age and co-morbidities.

Among initial antidepressants, flupentixol/melitracen was shown to be associated with higher odds of achieving sustained treatment-free status than SSRIs; this can be better understood in the context that only 15.9% of the patients initially prescribed flupentixol/melitracen in this study were cases with MDD. The finding that patients with depressive disorders not fulfilling the criteria for MDD were more likely to be prescribed flupentixol/melitracen is particularly relevant because a substantial proportion of out-patients in real-world settings were reported not to meet the criteria of minimum baseline severity for antidepressant efficacy trials and those with less severe depressive symptoms were associated with better outcomes (van der Lem *et al.* 2011).

Compared to patients prescribed SSRIs, those prescribed tricyclic antidepressants (TCAs) or other older-generation antidepressants had costs that did not differ

Table 4. *Multivariate analysis of total healthcare costs for the consecutive 3 years*

	First-year costs	Second-year costs	Third-year costs
Outcome status (*v.* late recontact)			
Sustained treatment-free status	1.051 (1.030–1.072)**	0.668 (0.652–0.684)**	0.777 (0.757–0.798)**
Continuous treatment	1.222 (1.199–1.246)**	1.087 (1.062–1.112)**	1.176 (1.147–1.206)**
Age group (years) (*v.* 18–24)			
⩾ 85	1.723 (1.619–1.834)**	2.737 (2.518–2.975)**	2.964 (2.694–3.261)**
75–84	1.469 (1.426–1.514)**	2.278 (2.194–2.365)**	2.409 (2.312–2.509)**
65–74	1.250 (1.218–1.283)**	1.892 (1.832–1.955)**	2.027 (1.957–2.099)**
55–64	1.080 (1.053–1.108)**	1.577 (1.528–1.626)**	1.699 (1.643–1.757)**
45–54	0.968 (0.946–0.990)**	1.339 (1.302–1.378)**	1.405 (1.363–1.448)**
35–44	0.935 (0.915–0.957)**	1.235 (1.202–1.270)**	1.295 (1.257–1.334)**
25–34	0.932 (0.910–0.954)**	1.191 (1.157–1.226)**	1.226 (1.188–1.265)**
Sex			
Male *v.* Female	1.090 (1.077–1.102)**	1.046 (1.031–1.060)**	1.067 (1.051–1.083)**
Depression type			
Major depression *v.* Other depression	1.079 (1.067–1.092)**	1.065 (1.050–1.080)**	1.074 (1.058–1.091)**
Past treatment history[a]			
Newly diagnosed depression	1.045 (1.031–1.058)**	0.980 (0.965–0.996)*	0.982 (0.966–1.000)*
Non-newly diagnosed depression with history of both AD treatment and depression diagnosis	1.079 (1.061–1.098)**	1.061 (1.038–1.084)**	1.061 (1.036–1.086)**
Physician type			
Non-psychiatrist *v.* Psychiatrist	1.035 (1.020–1.051)**	1.029 (1.010–1.049)**	1.028 (1.008–1.049)**
Clinical setting (*v.* In-patient)			
Out-patient	0.450 (0.436–0.465)**	0.671 (0.644–0.699)**	0.684 (0.654–0.716)**
Emergency service	0.672 (0.613–0.737)**	0.816 (0.728–0.915)**	0.779 (0.688–0.881)**
Index AD treatment (*v.* SSRI)			
SNRI	1.176 (1.153–1.199)**	1.079 (1.053–1.105)**	1.069 (1.041–1.097)**
Other newer AD[b]	1.119 (1.085–1.154)**	1.076 (1.036–1.118)**	1.024 (0.983–1.067)
TCA	0.906 (0.888–0.924)**	1.011 (0.986–1.037)	0.982 (0.956–1.009)
Other older AD[c]	0.950 (0.936–0.965)**	1.003 (0.984–1.022)	1.020 (0.999–1.041)
Flupentixol/melitracen	0.880 (0.856–0.905)**	1.007 (0.973–1.041)	0.978 (0.943–1.014)
Use of multiple ADs	1.120 (1.100–1.140)**	1.089 (1.065–1.113)**	1.082 (1.056–1.108)**
Presence of baseline physical illnesses			
Chronic obstructive pulmonary disease	1.093 (1.076–1.109)**	1.089 (1.069–1.110)**	1.131 (1.108–1.154)**
Diabetes mellitus	1.220 (1.199–1.242)**	1.278 (1.250–1.306)**	1.288 (1.258–1.319)**
Renal disease	1.178 (1.150–1.207)**	1.235 (1.198–1.273)**	1.251 (1.210–1.293)**
Cancer	1.291 (1.257–1.326)**	1.214 (1.173–1.257)**	1.259 (1.212–1.307)**
Cardiovascular disease	1.128 (1.113–1.143)**	1.117 (1.099–1.136)**	1.068 (1.049–1.087)**
Presence of baseline PPS			
Headache/migraine/dizziness	1.028 (1.016–1.040)**	1.031 (1.016–1.045)**	1.049 (1.032–1.065)**
Back	1.056 (1.043–1.069)**	1.029 (1.013–1.045)**	1.037 (1.020–1.054)**
Musculoskeletal	1.060 (1.048–1.073)**	1.076 (1.061–1.092)**	1.074 (1.058–1.091)**
Gastrointestinal	1.048 (1.036–1.060)**	1.029 (1.015–1.044)**	1.039 (1.024–1.055)**
Others	1.078 (1.056–1.099)**	1.049 (1.024–1.076)**	1.061 (1.033–1.090)**
Presence of baseline mental illnesses			
Schizophrenia	1.571 (1.530–1.613)**	1.745 (1.689–1.803)**	1.785 (1.723–1.848)**
Other psychotic disorders	1.074 (1.038–1.111)**	1.068 (1.024–1.114)**	1.155 (1.104–1.209)**
Substance related	1.224 (1.184–1.265)**	1.287 (1.235–1.341)**	1.328 (1.270–1.388)**
Alcohol related	1.369 (1.291–1.452)**	1.469 (1.364–1.582)**	1.553 (1.431–1.686)**
Drugs related	1.088 (1.012–1.170)**	1.033 (0.943–1.131)	1.070 (0.969–1.182)
Bipolar spectrum disorder	1.151 (1.111–1.194)**	1.176 (1.124–1.230)**	1.177 (1.122–1.235)**

Table 4 (*cont.*)

	First-year costs	Second-year costs	Third-year costs
Dementia	1.199 (1.166–1.234)**	1.226 (1.183–1.271)**	1.257 (1.208–1.308)**
GAD	0.983 (0.961–1.005)	0.957 (0.930–0.984)**	0.966 (0.937–0.995)*
Obsessive–compulsive disorder	1.031 (0.993–1.070)	1.034 (0.988–1.082)	1.084 (1.032–1.138)**
Panic disorder	0.923 (0.898–0.949)**	0.910 (0.880–0.942)**	0.957 (0.923–0.993)*
Phobic disorder	0.943 (0.892–0.997)*	0.974 (0.910–1.044)	0.936 (0.870–1.008)
Post-traumatic stress disorder	1.067 (0.954–1.193)	1.157 (1.009–1.326)*	1.295 (1.119–1.499)**
Sleep disorder	1.029 (1.016–1.042)**	1.047 (1.030–1.063)**	1.042 (1.025–1.060)**
Attention deficit hyperactivity disorder	0.890 (0.717–1.104)	0.978 (0.750–1.275)	1.024 (0.771–1.361)
Baseline total healthcare expenditures (in 1000 international dollars)	1.159 (1.155–1.162)**	1.161 (1.156–1.166)**	1.157 (1.151–1.162)**

AD, Antidepressant; SNRI, serotonin norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor; PPS, painful physical symptoms; GAD, generalized anxiety disorder.

[a] Reference group is non-newly diagnosed depression with history of either AD treatment or depression diagnosis.

[b] Bupropion and mirtazapine.

[c] Maprotiline, moclobemide and trazodone.

Values given as relative risk (99% confidence interval).

* $p<0.01$, ** $p<0.001$.

significantly in the second and third years whereas initial prescription of multiple antidepressants was associated with higher total costs in each of the 3 years. This is consistent with a previous systematic review that patients using TCAs generally had healthcare costs comparable to those using SSRIs in database studies (Pan *et al.* 2012). Our findings add to the evidence base by showing that, after taking into account initial outcome status, total healthcare costs do not differ between patients prescribed SSRIs and older-generation antidepressants over a longer-term follow-up but initial prescription of multiple antidepressants is associated with higher costs.

PPS

Patients with PPS have been shown to be less likely to achieve remission following acute treatment for depression (Fava *et al.* 2004), and our study concurs with these studies in finding that having certain PPS is associated with late recontacts even after a 6-month treatment-free status. Moreover, we previously found that the presence of baseline PPS consistently predicts higher 12-month healthcare costs of patients with depression (Pan *et al.* 2013*a*), consistent with prior studies that patients with PPS and depression had higher service utilization and costs (Gameroff & Olfson, 2006). The current findings also showed that the presence of each kind of PPS at baseline is associated with an increase in total healthcare costs, not only in the first year but also in the second and third years.

Co-morbid mental disorders

The presence of most co-morbid mental disorders was associated with decreased odds of having sustained treatment-free status and increased odds of staying on continuous treatment, with dementia being the only exception. Depressive symptoms in dementia rarely persist over a longer-term follow-up, for example 2 years (Aalten *et al.* 2005; Savva *et al.* 2009; Wetzels *et al.* 2010). Over time, depression has tended to decrease with a high resolution rate (Bergh *et al.* 2011) whereas apathy has increased in these patients (Aalten *et al.* 2005; Wetzels *et al.* 2010). Therefore, one possible interpretation of our results could be that depression occurs over certain stages in the course of dementia and disappears later when the illness progresses.

The presence of co-morbid mental disorders increased costs in the following years with the exceptions of GAD, panic and phobic disorder. Patients with anxiety disorders have been shown to be less likely to use services compared to those with mood disorders, and also to have reduced perceived need for help (Mojtabai *et al.* 2002; Alonso *et al.* 2004). Despite potential confounding from differences in coding systems, it seems probable that the lower service use and costs of these patients as seen in our study may be influenced by the nature of their co-morbid anxiety disorders. The extent to which the co-morbid anxiety disorders influences health-service use and costs of patients with depression warrants further research.

Implications and policy recommendations

Choice of index antidepressants between SSRIs and older-generation antidepressants did not show any significant differences in healthcare costs in the second and third years whereas prescription of multiple antidepressants at the index visit, although possibly influenced by physician preferences and the nature of the depressive disorders, was associated with higher total healthcare costs in the following years, implying that initial prescription of a single antidepressant may be preferable to constrain costs.

Patients not achieving sustained treatment-free status were found to have higher healthcare costs in the subsequent years in this study. As shown in a recent study (Pan *et al*. 2013*b*), patients remaining engaged with antidepressant treatment within the first 3 months after the index visit have higher odds of achieving sustained treatment-free status and lower odds of having late recontacts over the 18-month period. It seems that endeavors to reduce early attrition, probably through shared decision making and good patient–physician communication, and to improve initial treatment outcome of depression should be emphasized so to reduce total healthcare costs in the subsequent years.

Limitations

There are limitations to this study. As service-use data contained in the NHIRD include only information from health services provided by the NHI system in Taiwan, the perspective of the current analysis was limited, and we were not able to analyze wider economic impacts outside the health system. The lack of information on clinical symptoms and the use of a proxy definition are also limitations. We are aware that stopping a psychopharmacological therapy may have complex reasons other than achieving good clinical response, for example experiences of side-effects of medications. However, with the 18-month observation period in this study, the sustained treatment-free status seems likely to indicate initial treatment effectiveness without later clinical fluctuations sufficient to trigger a medical contact when simultaneously specifying another subgroup of subjects who have later recontacts, which may reflect changes in clinical conditions in which help-seeking is considered beneficial (Pan *et al.* 2013*b*).

Moreover, as this was a secondary analysis of a large healthcare database, we are aware that the analysis of the pattern of care and related costs of individual outcomes over time may require combining further information from other sources, such as bottom-up longitudinal studies of treated prevalence and prior expert knowledge, to give firmer conclusions. A replication study with a more recent cohort in Taiwan may also be warranted to reflect changes in healthcare systems over time, along with its associated impacts on subjects' service use and healthcare costs. Additionally, future research adopting a cost–incidence design may help to enhance our understanding of the impact of course of depression on service use and costs.

Factors that may further limit generalizability of the current findings include differences in the insurance system and the role of private health insurance between countries. In this study most patients with depression received specialized treatment from psychiatrists, and this is very different from countries in which the referral system is emphasized. Within the NHI system in Taiwan, patients can easily have access to specialists without referrals from general practitioners and with affordable co-payments. Therefore, this unique medical environment of Taiwan should be borne in mind when interpreting the current results.

Conclusions

This study, based on a large national cohort, indicates that the outcome status of initial treatment exerts an impact on total healthcare costs in the second and third years after the index date. Furthermore, the presence of co-morbid anxiety disorders and PPS had an impact on the total healthcare costs of patients with depression over the longer-term follow-up. It is important to both physicians and policy makers to further improve initial treatment outcomes of depression through effective strategies. Future endeavors to explore the impacts of co-morbid anxiety disorders and PPS on health service use and treatment of depression are warranted.

Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291713001700.

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Declaration of Interest

M.K. has acted as consultant and speaker for Lundbeck and Bristol Myers Squibb, and has had research funding from Janssen. P.M. has received speaker and consultancy fees from Lundbeck, Bristol Myers Squibb, Lilly and Janssen-Cilag.

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